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The New England Journal of Medicine

FORMERLY THE BOSTON MEDICAL AND SURGICAL JOURNAL — *Established 1828*

VOLUME 248 . APRIL 16, 1953 . NUMBER 16

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Entered as second-class matter, November 16, 1932, at the post office at Boston, Massachusetts, under the Act of March 3, 1879. Published weekly at 8 Fenway, Boston 15. Domestic, $8.00 per year.

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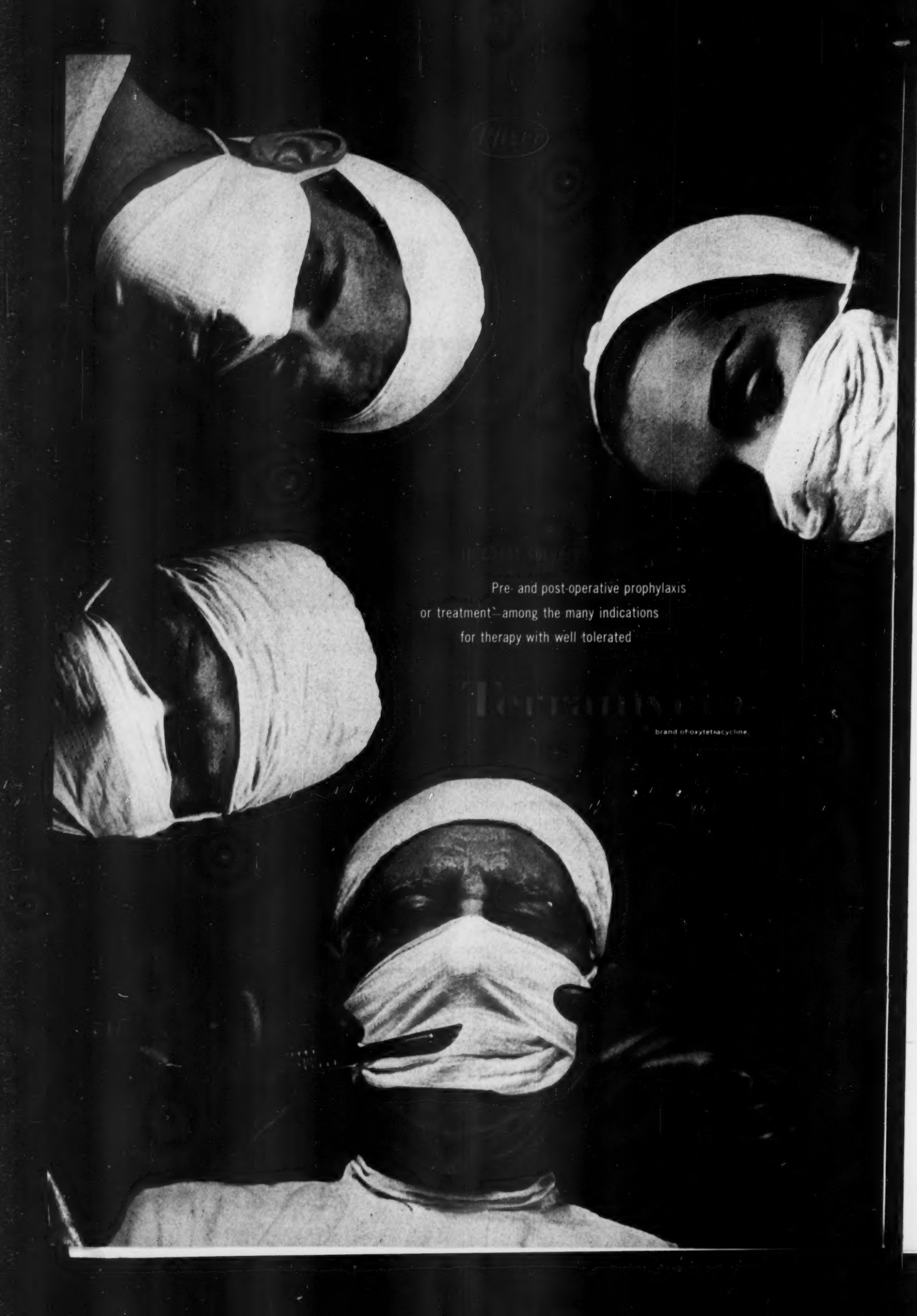
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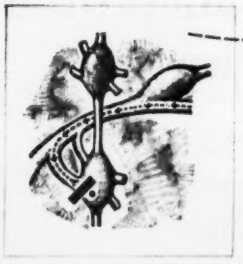

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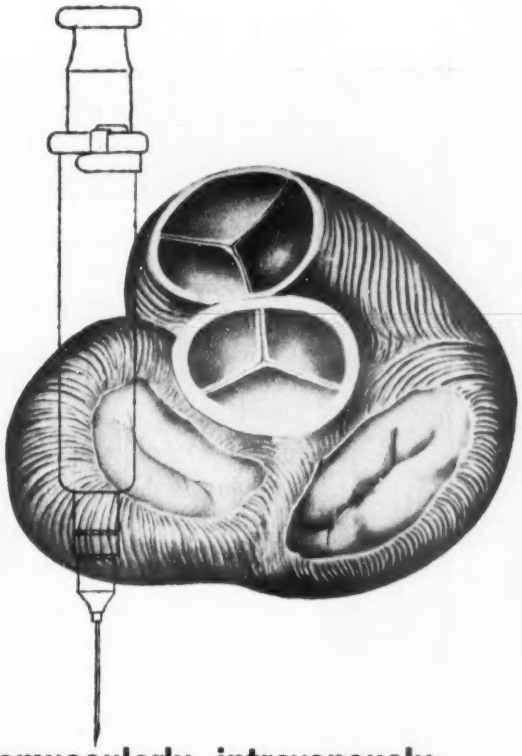

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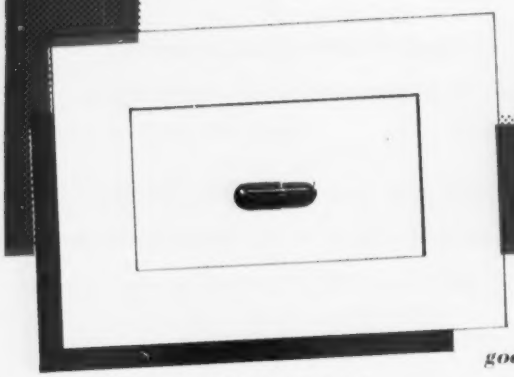

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Volume 248 APRIL 16, 1953 Number 16

WHIPPLE'S DISEASE*

Report of a Case with Special Reference to Histochemical Studies of Biopsy Material and Therapeutic Results of Corticosteroid Therapy

CHESTER M. JONES, M.D.,† JOHN A. BENSON, JR., M.D.,‡ AND AGUSTIN L. ROQUE, M.D.§

BOSTON

IN 1907 Whipple[1] first described intestinal lipodystrophy, an entity that has since been recorded but 37 times. Theories of the pathogenesis of the lipogranulomatosis of the small intestine and mesenteric lymph nodes have failed to suggest an effective form of therapy. The majority of reported cases have occurred in males, and most of the patients have died after a debilitating course of abdominal pain, steatorrhea, malnutrition with striking pigmentation and arthritis, despite various forms of treatment, including bile salts, pancreatic extract, choline, lecithin, folic acid, liver extract, aqueous adrenocortical extract, desoxycorticosterone, duodenal fluid, the fat-soluble vitamins and supportive measures.

Whipple himself pointed out that although there were excessive fatty acids in the ileal tissue on chemical analysis, the cytoplasmic vacuoles in the foamy cells showed little or no fat-staining material. In 1949 Black-Schaffer[2] found that these cells stained not with Sudan IV, osmic acid or Nile-blue sulfate but with the periodic-acid-Schiff reaction. Thus a glycoprotein was implicated rather than lipoid material in a process that he regarded as an obscure defect in fat metabolism with disturbed epithelial function. Because of the rheumatic and serous-membrane manifestations in the course and pathology of this disease, it has recently been considered as a connective-tissue or collagen disease.[3] Although no lesions typical of the rheumatic state have been described in the small intestine, the hypothesis was advanced that an altered reactivity to some unknown agent disturbed epithelial function.

The case of Whipple's disease presented below is unusual both because the patient is a woman and because all clinical manifestations of her illness disappeared after therapy with ACTH and cortisone. She has apparently maintained her remission for ten months without further treatment.

*The histologic studies were partly supported by an institutional grant from the American Cancer Society to the Massachusetts General Hospital.

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‡Research fellow in medicine, Harvard Medical School; clinical and research fellow in medicine, Massachusetts General Hospital; fellow, Dazian Foundation for Medical Research.

§Research fellow in pathology, Massachusetts General Hospital.

CASE REPORT¶

On September 19, 1951, a 49-year-old housewife of French-Canadian extraction, was admitted to the hospital with the probable diagnosis of sprue. She had had intermittent epigastric distress, with occasional nausea and vomiting, for 20 years. Two years before admission she had suffered a typical attack of rheumatoid arthritis in the right hip, fingers and ankles, which was treated with gold injections for 5 months. Subsequently, she suffered an attack of right-sided pleurisy. Thirteen months before entry cholecystectomy was performed because of increasingly frequent and severe attacks of epigastric pain. The well tolerated removal of a noncalculous gall bladder gave only 5 months' respite. Recurrent right epigastric and subcostal pain became sharper and often awoke the patient from sleep. Insidiously, 4 months before admission, loose, foamy stools with lower abdominal cramps and tenesmus began, with steady progression and severe abdominal distention. At another hospital, thickened duodenal and jejunal folds and unusual segmentation in the terminal ileum were visualized on x-ray study. Deepening pigmentation was noted. A 4-hour epinephrine test was negative (fasting eosinophil count of 19 per cubic millimeter), as was a Kepler-Power water test. Only 2.9 mg. of 17-ketosteroids was excreted in a 24-hour urine. Intensive therapy with folic acid and liver along with less specific measures failed to stem the now rapid progression of the symptoms and malnutrition. The patient had lost 25 pounds during the preceding 4 months and weighed finally 99 pounds. She had had bowel movements as frequently as once an hour.

Physical examination revealed a thin, emaciated, weak, dehydrated woman, whose dry, scaly skin was strikingly pigmented with a yellowish-brown diffuse cast, most marked in the palmar creases and in operative scars. There was no oral pigmentation or jaundice. The blood pressure was 120/50, and the heart was not small. There was diffuse abdominal tenderness and distention. No masses or organs were palpated. The joints presented no objective evidence of disease. There were no other physical findings of diagnostic importance.

Laboratory examination demonstrated a microcytic anemia, hypoproteinemia, excessive stool fat and low normal enzymatic activity in the duodenal fluid. Examination of the blood showed a red-cell count of 3,260,000, with a hemoglobin of 9.0 gm., a hematocrit of 24 per cent and a mean corpuscular volume of 73 cubic microns, and a white-cell count of 10,900, with 94 per cent neutrophils and a fasting eosinophil count of only 9 per cubic millimeter. Blood chemical findings included a total protein of 4.77 gm. (with an albumin level of 2.97 gm.), calcium of 7.8 mg., alkaline phosphatase of 9.6 Bodansky units and serum amylase of 23 Somogyi units per 100 cc., and a normal prothrombin time. Serum sodium, potassium and chloride concentrations were normal. Urinalysis and a blood Hinton test were negative. Fasting gastric

¶This case was previously reported, in less detail,[4] and presented at a meeting of the Association of American Physicians, May, 1952.

juice showed no free hydrochloric acid. No tumor cells were discovered in a cytologic examination of the duodenal drainage. The duodenal contents collected 45 minutes after the ingestion of 50 cc. of 20 per cent cream disclosed an amylase of 74 Russell units per 100 cc., lipase of 32.6 cc. and tryptic activity of 35 per cent; these were low normal values. The stools were at first guaiac negative, and microscopical examination demonstrated increased fatty acids and split fat combinations but no undigested muscle fibers or excessive neutral fat. Analysis of a 3-day collection revealed that 23.05 gm. of fat (50 per cent of oral intake) and 2.69 gm. of nitrogen were being excreted daily in the stools. A gastrointestinal series showed a typical "deficiency" pattern; barium reached the cecum in 3 hours. Barium-enema and sigmoidoscopic examinations were negative. Dextrose, vitamin A and fat tolerance tests were thwarted by vomiting, so that pretreatment control values were not possible. Orally administered carmine appeared in the stool in 2 3/4 hours.

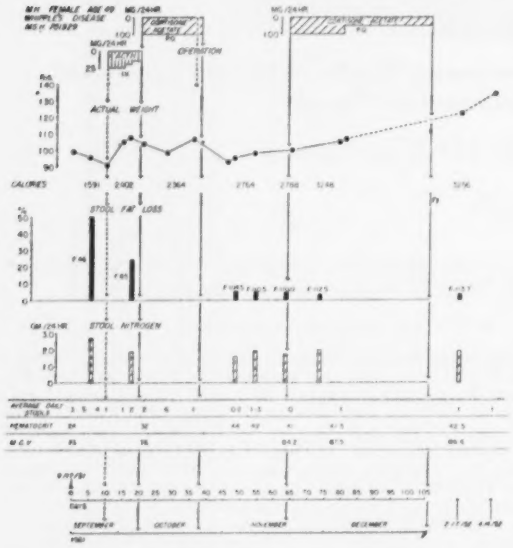

FIGURE 1. *Effect of Cortisone and ACTH.*
The stool fat loss is represented as the percentage loss of the daily dietary intake of fat. The figures beside each column represent grams of fat intake per day.

The increasing severity of symptoms and further weight loss during the period of investigation (Fig. 1), even with supportive therapy and 2 transfusions, made more active treatment imperative. Because of the success in treatment of similar symptoms in patients with nontropical sprue, adrenocorticotrophic hormone was started on September 27, 1951, 200 mg. being given over 10 days by slow intravenous drip. Within 3 days the patient noted an increase in appetite, weight and strength. On the 6th day distention had nearly disappeared, but puffy rounding of the face and ankle edema developed. Stools were becoming less frequent and firmer. By the 10th day she had gained weight from 91 to 106½ pounds and was comfortably eating over 2300 calories daily. Nausea and vomiting had disappeared, and clinical improvement was dramatic. The fecal fat loss had fallen to 15.77 gm. per day or 24.3 per cent of ingested fat, and stool nitrogen to 1.88 gm. per day. On October 7 cortisone acetate, 100 mg. daily by mouth, was substituted for the ACTH because oral therapy was considered less troublesome to the vastly improved patient. A diuresis of 7 pounds ensued, and she became mildly constipated. At the peak of the diuresis, after 3 days of cortisone therapy, serum electrolyte concentrations were normal; the serum calcium had risen to 9.6 mg. per 100 cc. without supplementary calcium therapy, the total protein to a level of 5.46 gm., and the albumin to 3.75 gm. per 100 cc. of serum.

On continued oral cortisone therapy, the diarrhea remained checked, but a curious 4-day acute "surgical" episode, suggesting perforation of an abdominal viscus, and persistent melena forced the decision to operate to establish an absolute diagnosis and to exclude focal intestinal disease. The patient had regained weight to the previous level of 106½ pounds.

On October 23, with the preoperative diagnosis of Whipple's disease, Dr. Richard Warren performed a laparotomy. About 1200 cc. of chylous ascitic fluid was first encountered. The presenting disease was a marked lymphadenopathy in the entire distribution of the superior mesenteric artery. Yellowish-white, succulent lymph nodes, ranging from the size of a pea to 3 cm. in diameter, were present in a confluent manner in the whole mesentery of the jejunum and upper ileum, the process seeming to stop in the ileomesentery about 30 cm. above the ileocecal valve. The bowel in the affected areas was thickened and laced with milky, distended lymphatics running down over the mesentery. Over the antemesenteric surfaces of the bowel the lymphatics assumed small varicose forms, and there were scattered milky plaques representing subserosal rupture and leakage of chyle. The process was most marked at the ligament of Treitz, diminishing gradually over the remaining extent of involved bowel. There was no evidence of perforation or peritonitis. From the mesentery of the lower jejunum a lymph node was removed, from which squeezing expressed a creamy material. A biopsy of the jejunal wall just below the ligament of Treitz was made. A wedge resection of 5 cm. of ileum, including its mesentery, was also performed, the defect being successfully reconstituted by an end-to-end anastomosis. The ascites was teeming with chylomicrons (index of 456) on dark-field microscopic examination and contained 340 mg. of total lipids per 100 cc.

The postoperative course was remarkably uneventful. Cortisone was discontinued after the 1st postoperative day, after a total 2 weeks' course of 1250 mg. Stools were formed and normal in appearance. It was now obvious that the pigmentation had been gradually fading. The patient was transferred to the metabolic ward, where studies were begun on November 4, the 12th postoperative day.

Two consecutive 6-day balance periods, the 2d with placebos resembling cortisone, revealed that the stools contained 5.52 gm. of fat and 1.58 to 1.92 gm. of nitrogen daily. This represented a normal loss of only 5.2 per cent of ingested fat. A steady weight gain on a constant dietary intake of 2764 calories per day (protein of 117.5 gm. and fat of 107.5 gm.) ensued, along with a continuous rise toward normal in hemoglobin, red-cell count and indexes, and serum albumin.

Oral tolerance tests were performed during this control study before and after the collection periods, 30 cc. of olive oil, 200,000 units of vitamin A (oleum percomorphum) and 100 gm. of dextrose as a lemonade being given as the test meal and the serum serially sampled. Immediately after the 4th hour of the test, the usual hospital lunch was served.

TABLE 1. *Results of Oral Tolerance Tests.*

DATE	GLUCOSE TOLERANCE					VITAMIN A TOLERANCE				
	0 HR.	½ HR.	1 HR.	2 HR.	3 HR.	0 HR.	3 HR.	4 HR.	5 HR.	6 HR.
	mg./100 cc.	*mg./100 cc.*	*mg./100 cc.*	*mg./100 cc.*	*mg./100 cc.*	*units/cc.*	*units/cc.*	*units/cc.*	*units/cc.*	*units/cc.*
11/2/51	82	84	84	91	112	0.97	1.90	1.51	4.81	3.13
11/16/51	72	122	161	76	135	0.68	1.76	2.09	—	3.35
11/26/51	59	220	187	82	156	1.24	1.56	3.29	—	4.43
2/7/52	88	152	180	107	63	1.32	1.87	1.28	3.30	2.00

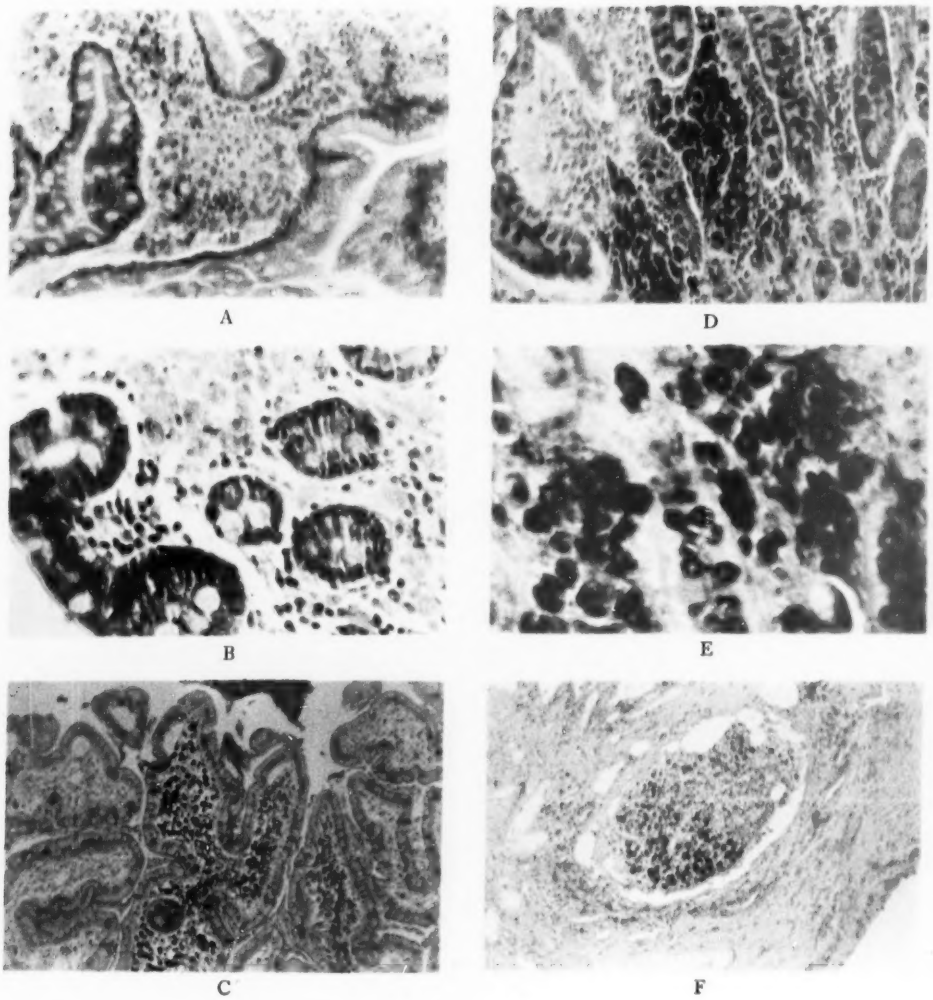

FIGURE 3. *Sections of Jejunum and Mesenteric Node.*

A = *hematoxylin and eosin stain of mucosa, showing pink-staining monocytes in the tunica propria.*

B = *toluidine-blue preparation, showing the metachromasia (pale cells between the glands).*

C = *periodic-acid-Schiff (P.A.S.) preparation, showing a positive reaction within the monocytes of the tunica propria. (Note also the positive reaction in the mucus within the lumen.)*

D = *a higher magnification of the P.A.S. preparation, showing the positive reaction in the monocytes and also in the goblet cells of the intestinal glands.*

E = *P.A.S. and Sudan-black preparation, showing only a few sudanophilic granules (stained black) in and around the P.A.S.-positive monocytes.*

F = *P.A.S. preparation of a mesenteric lymph node, showing the positive reaction in the monocytes. (Note the dilated lymphatic channels, which proved to be filled with neutral fat.)*

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Blood glucose, total lipids (lipokrit[5]), vitamin A[6] and an index of photographed chylomicrons* were measured (Table 1). The initial dextrose tolerance test was flat, but the 3 curves of fat tolerance test (chylomicron index, lipokrit and vitamin A) were entirely normal, both on November 2, the 10th postoperative day, and on November 16.

Cortisone, 100 mg. daily, was then resumed, and after proper stabilization another balance period on the same diet intervened. The patient then lost but 4.5 per cent of ingested fat and 1.74 gm. of nitrogen daily in the stools. The corrected erythrocyte sedimentation rate fell from 1.22 to 0.7 mm. per minute, and the fasting eosinophil count from 77 to 37 per cubic millimeter. Thereupon the daily dietary intake was increased to 3248 calories by augmentation of only the carbohydrate and protein moieties, with a loss of but 3.4 per cent of dietary fat. On cortisone the oral dextrose tolerance test became somewhat diabetic. The serum vitamin A had shown a greater increase in 3 hours, suggesting better absorption. Although the chylomicron index and lipokrit rises after the test meals of olive oil had not changed significantly, the curves were considered within normal limits after cortisone.

Along with the tolerance tests described above, the serum lipid fractions before and after 10 days of cortisone administration were also determined (Table 2). The control test meal effected no rise in the total lipids or any of the fractions measured. Cortisone elevated the fasting level of all fractions measured, as well as the response of serum fatty acids to the test meal.

Five days after this 2d course of cortisone was started an acute episode of nondeforming rheumatoid arthritis of the left ankle developed, with consistent x-ray changes. This inflammation with mild effusion subsided in a few days.

On December 5 the patient was asymptomatic and weighed 105½ pounds. The hemoglobin was 12.6 gm. per 100 cc., the red-cell count 4,740,000, the hematocrit 41.5 per cent, and the mean corpuscular volume 87.5 cubic microns. The serum calcium was 10.2 mg., the total protein 6.58 gm., and the albumin 4.34 gm. per 100 cc. The cortisone dosage was reduced to 50 mg. per day and continued through December 31. The pigmentation had largely disappeared, even from the operative scars. Cortisone was then discontinued.

The patient was readmitted to the hospital in February, 1952, because of an acute rheumatoid process in the right ankle, which quickly subsided on aspirin, hot soaks and rest. The blood counts had improved even more, the hemoglobin being 13.7 gm. per 100 cc. and the red-cell count 4,905,000. The normal serum proteins, calcium and prothrombin time remained unchanged. On a diet of 3256 calories and 113.7 gm. of fat each day, her weight had increased to 122 pounds, and her daily formed stool contained 3.4 per cent of the ingested fat. Oral tolerance tests were normal. The fasting serum total lipid had fallen to 660. A glycine tolerance test,[10] employing 50 gm. of gelatin, indicated normal absorption of protein.

The patient has been seen periodically since. On October 21, she appeared in robust health, weighing 144 pounds, and had no gastrointestinal or other complaints. Blood counts and sedimentation rate remained normal, and there was no excessive fat on microscopical study of the stool. Thus she had enjoyed almost 12 months of good health and normal activity, 10 of them without therapy, and had gained overall 53 pounds.

TABLE 1 (*Concluded*).

DATE	CHYLOMICRON INDEX							LIPOKRIT							THERAPY
	0 HR.	1 HR.	2 HR.	3 HR.	4 HR.	5 HR.	6 HR.	0 HR.	1 HR.	2 HR.	3 HR.	4 HR.	5 HR.	6 HR.	
								mm.² %	mm.² %	mm.² %	mm.² %	mm. ² %	mm.² %	mm.² %	
11/ 2/51	35	15	150	528	168	324	144	700	680	680	920	728	900	764	Control
11/16/51	15	—	25	91	136	—	480	576	—	528	588	596	—	604	Control
11/26/51	23	—	54	65	23	264	468	720	—	700	644	660	780	800	Cortisone
2/7/52	3	5	73	23	176	720	96	660	—	616	644	672	868	696	Control

*To obtain a chylomicron index drops of serum were placed on a thin glass slide, and a coverslip pressed down firmly. With an electronic flash exposure, the field of chylomicrons, focused under dark-field microscopy, was photographed. Counts of 3 photographs of each specimen were made from projection on a standard grid, and the highest count was taken as the index for that serum. The average fasting level was 38, and 3 hours after the ingestion of 30 cc. of olive oil the average level was 121 in a series of 20 normal subjects.[9]

The histopathological findings in the jejunum and ileum† differed only in degree. The epithelium was intact, on ordinary hematoxylin and eosin staining (Fig. 2). Scattered throughout the entire tunica propria were large mononuclear cells with small nuclei and much pink-staining foamy cytoplasm (Fig. 3*A*). The bowel lymphatics were somewhat distended but not cystic. Eosinophils were present, but no foreign-body giant cells were observed. There was no evidence of a vasculitis in the resected specimens of small bowel or mesentery.

The granules or droplets of the cytoplasm of the large mononuclear cells were refractile but colorless in unstained preparations and showed no birefrigency when examined with the polarizing microscope. Employment of a battery of histochemical tests characterized the material in these foamy cells as water insoluble, basophilic, metachromatic (Fig. 3*B*), and strongly positive with periodic-acid-Schiff reagent (P.A.S.) (Fig. 3*C* and 3*D*). Aniline blue stained it to the same degree as it did adjacent connective tissue. This substance was not digested by saliva, and hence is not glycogen. Digestion with hyaluronidase was also negative, although this test was performed on formalin-fixed tissue. The fat stains did not stain the material. Strands of interstitial material, the mucin of the goblet cells, and free mucin in the intestinal lumen also took the P.A.S. stain.

Sudanophilic lipid droplets were notable for their sparse and interstitial distribution in the tunica propria. Sudan IV and Sudan Black did stain a few fine droplets in these large macrophagic cells (Fig. 3*E*), but most of the lipoids were extracellular or in the lacteals. They also showed no birefringency, and the digitonin test was negative, the presence of cholesterol complexes being eliminated. Nile-blue sulfate stained these lipoid droplets a bright pink, revealing the presence of neutral fats or unsaturated triglycerides.

The lymph node showed markedly distended lymphatics and the same large cells containing P.A.S.-positive granules in their foamy cytoplasm (Fig. 3*F*). The lymphatics here were filled with fat, and other large phagocytes were laden with neutral fat. The lymphoid tissue was somewhat displaced by these foamy cells. There was no evidence of chronic inflammation.

The liver biopsy was negative. There was a mild infiltration with neutral fat in the periphery of the lobules.

SIGNIFICANCE OF THE HISTOPATHOLOGY

Whipple[1] was unable to stain the cytoplasmic vacuoles in the foamy cells of the submucosal layer with osmic acid, which is said to oxidize and polymerize only unsaturated fatty acids. He described these foamy cells as being "in the neighborhood of fat deposits." His distinction between these lipid-free unusual macrophages and the large fat vacuoles in the submucosa and lymph nodes has apparently been largely ignored. Black-Schaffer[2] renewed interest in this material by first demonstrating its positive reaction with the P.A.S. (periodic-acid-Schiff) reaction. Since P.A.S. can oxidize the 1–2 glycol bond of polysaccharides to produce stainable

†We are indebted to Dr. Benjamin Castleman, head of the Department of Pathology, Massachusetts General Hospital, for assistance in reviewing the pathology.

polyaldehydes, he likened this substance to the glycoprotein of mucin. But he, too, was unable to demonstrate the presence of glycogen with Best's carmine. He also stated that the material was

FIGURE 2. *Low-Power Photomicrograph, Showing Intact Mucosa.*

Note the edema and dilated lymphatics in the submucosa.

neither steroid nor phospholipid. Upton[11] found positive mucicarmine and negative amyloid-staining reactions. Basophilia, metachromasis and positive P.A.S. reactions are characteristic of polysaccharides but are not specific since lipids and proteins also have these properties. Black-Schaffer postulated that this substance is an abnormally absorbed enteric mucin. It is conceivable that it may be a polysaccharide from connective tissue. A silver (Ortega) stain of a paraffin section of our material revealed a normal epithelial basement membrane and reticulum of the lamina propria of the small intestine. Presumably, the substance did not derive from degeneration of reticulum. Aniline blue stained the material as it did connective tissue elsewhere in the section. One of us (A. L. R.) has similarly studied a case of tropical sprue, in which there was a normal reticulum stain and no P.A.S.-positive material in the small bowel.

Kampmeier and Peterson[3] and other authors[12] have offered the possibility of classifying Whipple's disease as a collagen or connective-tissue disease on the basis of clinical similarities. But to date we have observed no P.A.S.-positive material in the cells of the small intestine of a few patients with scleroderma, rheumatoid arthritis and disseminated lupus erythematosus. The foamy cell has never been described in the bowel in such diseases. Thus the question of whether this P.A.S. substance derives from connective tissue as a result of another collagen disease remains unanswered. Unfortunately, at the present time there are no histochemical tests available to characterize the polysaccharides of different tissues — for example, to distinguish between a glucuronate of mucin and a hyaluronate of connective tissue. Finally, it is possible that these mononuclear cells contain a lipoprotein, which would be Schiff-positive but would not take any of the fat stains — a condition analogous to that of the Gaucher cell. This cell contains kerasin, a galactolipoprotein that is also Schiff positive.[13]

It must be remembered that our case was studied histochemically after the administration of ACTH and cortisone had improved intestinal absorption. These beneficial drugs could have altered the picture. Yet our findings seem to be consistent with those of Black-Schaffer's 4 untreated autopsied cases.[14] Furthermore, we have performed the same histochemical studies on tissue kindly submitted from the case reported by Plummer et al.[12] This patient had not been treated with corticosteroids, and the jejunum and spongy lymph node showed staining reactions identical to those noted above.

TABLE 2. *Serum Lipid Fractions.*

DATE	HOUR OF TEST	CHOLESTEROL*	TOTAL FATTY ACIDS*	LIPID PHOSPHORUS*	LIPOKRIT
		mg./100 cc.	*mg./100 cc.*	*mg./100 cc.*	*mm.²%*
11/16/51 (before cortisone therapy)	0	259.5	408.5	11.1	576
	2	246.5	381.7	11.0	528
	3	235.8	376.0	10.9	588
	4	235.8	407.6	10.8	596
	Lunch				
	6	223.8	414.2	11.1	604
11/26/51 (during cortisone therapy)	0	312.1	436.1	12.5	720
	2	309.6	488.3	13.0	700
	3	278.3	439.7	12.0	644
	4	273.1	475.7	12.0	660
	Lunch				
	6	266.5	533.3	14.0	800

*We are indebted to Dr. J. Folch-Pi, of McLean Hospital, for these determinations.

Another untreated case has recently come to our attention with P.A.S.-positive material in a mesenteric node.[15] This untreated case is of greater interest because of the lack of steatorrhea at the time of biopsy.

Discussion

Our belief is that this evidence may point toward an underlying and fundamental metabolic disturbance in the primary function of the intestinal mucosa. The rapid response of improved intestinal absorption in otherwise refractory cases of sprue given corticosteroids[16-18] provides a somewhat analogous field for speculation. In each disease, ordinary stains demonstrate an apparently normal epithelium. The abnormal polysaccharide deposits in the pathways of fat absorption suggest a metabolic disorder. The normal pancreatic ferments and failure of previous therapies with bile salts, duodenal fluid, hydrochloric acid, pancreatic extracts, choline and so forth[19] indicate that digestion per se was adequate. And, as demonstrated by the weight gain, normal chylomicrons, positive nitrogen balance and normal oral dextrose tolerance tests, once the nutrients reach the circulation, they appear to be normally utilized by the body. In our improved patient heparin, 35 mg. administered intravenously, promptly cleared the serum of alimentary lipemia; the chylomicron index fell from 348 to 6, and the lipokrit from 848 to 756 cubic millimeters per cent in twenty minutes. This unexplained phenomenon is likewise that of the normal person. Both Whipple[1] and Black-Schaffer[2] have also implicated such an obscure defect in intestinal epithelial metabolism.

There are other theories of pathogenesis.[12] A foreign-body reaction to some absorbed toxic material is one concept. A lecithinase from intestinal clostridia can cause flocculation and deposition of fat in vitro. The production of a specific antibody in a case of mesenteric chyladenectasis has been demonstrated.[12] Local fat necrosis, yielding lipolytic ferments, and faulty resynthesis of triglycerides, leading to an accumulation of irritative free fatty acids and resultant fibrosis, have been postulated. None of these concepts are borne out by the pathology in the 2 cases studied by us.

We do not know whether the thoracic duct was obstructed in the case presented above but strongly doubt it. Only 6 reported cases have been thoroughly studied to exclude this possibility. Hendrix et al.[14] believe that any case with evidence of chylous obstruction, such as dilated bowel lymphatics, cannot properly be diagnosed as Whipple's disease. This restriction excludes Whipple's original description. The macrophagocytosis of the bowel and the lipogranulomatosis of the affected lymph nodes may eventually tend to obliterate lymphatics and thereby obstruct fat absorption mechanically. Perhaps mobilization by the corticosteroids of the substance in the stuffed foamy cells, much as these agents clear an inflammatory exudate, is partially responsible for the improvement noted in our patient. A reduction in submucosal swelling may have contributed to better drainage of the lymphatics. We observed no chylangiectasis, lymphangitic scarring, lacteal fibrosis or thickening of the capsule of the lymph node that might have obstructed the efferent lymph radicle. Furthermore, absorption of foodstuffs had approached normal by the time the biopsies were obtained from the thickened gut with its engorged lymphatics and prominent foamy cells, and ten days later fat absorption, as determined by the olive oil and vitamin A tolerance test curves, was normal. Bloor[20] found no rise in serum fatty acids after a test meal had been given to dogs whose thoracic ducts had been ligated. Our patient showed the same phenomenon. Our technics have demonstrated similar findings in 3 patients with proved obstructed thoracic ducts that had led to chylous effusions; indeed, these effusions had collected the absorbed fat and vitamin A. Thus it appears that any obstruction to lymphatic flow had occurred locally in the submucosa or lymph nodes in multiple scattered areas by compression from the abundant P.A.S.-positive macrophages and not from intrinsic lymphatic disease.

As the remission fully developed, the coarsened mucosal folds of the small bowel and the deficiency pattern disappeared, leaving an x-ray appearance indistinguishable from the normal picture. Also, the biopsied epithelium was intact and showed no jejunoileitis. Neither active inflammation nor fibrosis from a remote process seems responsible for the pathology of this disease. We do not agree with those[21] who suggest that Whipple's disease results from an inflammatory process similar to the lymphedema of regional ileitis.

The adrenal glands play a role in fat metabolism,[22] although there is evidence that they are not essential to either fat absorption[23, 24] or intestinal phosphorylation.[25] Our patient presumably had normal adrenal glands, as the reported patients who came to autopsy have had. Her four-hour epinephrine test showed a normal fall in circulating eosinophils. The fasting counts were low, and the water test was negative. The low urinary 17-ketosteroid excretion can probably be attributed to chronic debilitation, as can the lipoid depletion of the adrenal cortex sometimes reported in the literature. Furthermore, she responded dramatically to adrenocorticotrophic hormone. Her disease, therefore, cannot be attributed to adrenal insufficiency, despite the pigmentation, weakness, steatorrhea and the usual hypotension. Notable steatorrhea is not a constant finding in Addison's disease. On the other hand, the exhaustion phase of the general adaptation syndrome may be present with a "functional" adrenal insufficiency.

Adrenocortical hormones previously have been employed in the therapy of Whipple's disease.

Desoxycorticosterone has effected no appreciable change.[21, 26] Adrenocortical extract may have temporarily benefited 2 cases[21, 27] but not 3 others.[11, 14, 19] Compound A decreased the mild fecal fat losses of adrenalectomized rats maintained on desoxycorticosterone acetate and of Addison's disease in human beings.[28] The advent of ACTH, with its powerful adrenal-stimulating properties, and of cortisone, with its apparent specificity, has provided a dual opportunity for therapy. The systemic benefits of increasing well-being and appetite, the antirheumatic property and the lightening effect on pigmentation constitute appropriate empirical help. In addition, the corticosteroids appear to exert some metabolic influence on the intestinal epithelial cell to improve absorption.

These agents have in this case effected the first — to our knowledge — therapeutically induced remission reported in Whipple's disease, interrupting a rapidly downhill course that seemed destined to terminate quickly in death. The stress of a surgical operation, which can evoke a considerable pituitary-adrenal discharge, may have played a role in the apparent remissions of the 3 disputed cases of Pemberton et al.[29] and the fourth case of Kampmeier and Peterson.[3] However, in our case, an appreciable lessening of symptoms and steatorrhea after only several days of ACTH occurred before the operation. The dramatic rapidity of the response coincident with ACTH therapy leaves little room for believing that our patient's remission was spontaneous.

The occurrence of rheumatoid arthritis, pleuritis and response to the steroids suggests that Whipple's disease is another connective-tissue disease. The histochemical data are not inconsistent. We cannot, however, escape the conclusion that the corticosteroids have somehow profoundly altered, by a pharmacologic action, a metabolic defect localized in the intestinal epithelium.

At the time of publication of this article the patient has been clinically in excellent health for a total of 17 months.

Summary

The case of a woman with Whipple's disease, proved by biopsy showing characteristic histochemical reactions, who achieved a complete twelve months' remission after corticosteroid therapy is presented.

References

1. Whipple, G. W. Hitherto undescribed disease characterized anatomically by deposits of fat and fatty acids in intestinal and mesenteric lymphatic tissues. *Bull. Johns Hopkins Hosp.* **18**:382-391, 1907.
2. Black-Schaffer, B. Tinctoral demonstration of glycoprotein in Whipple's disease. *Proc. Soc. Exper. Biol. & Med.* **72**:225-227, 1949.
3. Kampmeier, R. H., and Peterson, J. C. Whipple's disease: its relationship to rheumatic state. *Tr. Am. Clin. & Climatol. A.* **61**:248-270, 1949.
4. Case Records of the Massachusetts General Hospital (Case 38101). *New Eng. J. Med.* **246**:375-381, 1952.
5. Herrmann, L. G., Ames, A., and Tapke, R. J. Observations upon lipokrit method for determination of lipoid content of blood. *J. Lab. & Clin. Med.* **19**:411-421, 1933.
6. May, C. D., Blackfan, K. D., McCreary, J. F., and Allen, F. H., Jr. Clinical studies of vitamin A in infants and in children. *Am. J. Dis. Child.* **59**:1167-1184, 1940.
7. Point, W. W. Unpublished data.
8. Bloor, W. R. Determination of cholesterol in blood. *J. Biol. Chem.* **24**:227-231, 1916.
9. Stoddard, J. L., and Drury, P. E. Titration method for blood fat. *J. Biol. Chem.* **84**:741-748, 1929.
10. Christensen, H. N., and Shwachman, H. Determination of plasma glycine after gelatin feeding as diagnostic procedure for pancreatic fibrosis. *J. Clin. Investigation* **28**:319-321, 1949.
11. Upton, A. C. Histochemical investigation of mesenchymal lesions in Whipple's disease. *Am. J. Clin. Path.* **22**:755-764, 1952.
12. Plummer, K., Russi, S., Harris, W. H., Jr., and Caravati, C. M. Lipophagic intestinal granulomatosis (Whipple's disease): clinical and pathologic study of thirty-four cases, with special reference to clinical diagnosis and pathogenesis. *Arch. Int. Med.* **86**:280-310, 1950.
13. Morrison, R. W., and Hack, M. H. Histochemical studies in Gaucher's disease. *Am. J. Path.* **25**:597-603, 1949.
14. Hendrix, J. P., Black-Schaffer, B., Withers, R. W., and Handler, P. Whipple's intestinal lipodystrophy: report of 4 cases and discussion of possible pathogenic factors. *Arch. Int. Med.* **85**:91-131, 1950.
15. Gross, J. B. Personal communication.
16. Adlersberg, D., Colcher, H., and Drachman, S. R. Studies on effects of cortisone and pituitary adrenocorticotropic hormone (ACTH) in sprue syndrome. *Gastroenterology* **19**:674-697, 1951.
17. Taylor, A. B., Wollaeger, E. E., and Comfort, M. W. Effect of cortisone on nontropical sprue: (idiopathic steatorrhea). *Gastroenterology* **20**:203-228, 1952.
18. Jones, C. M. Sprue syndrome: current concepts of condition with special reference to therapeutic effect of corticosteroids. Presented before the Second International Congress of Internal Medicine, London, September, 1952.
19. Reveno, W. S. Intestinal lipodystrophy (Whipple's disease): report of case. *New Eng. J. Med.* **243**:216-220, 1950.
20. Bloor, W. R. Studies on blood fat. I. Variations in fat content of blood under approximately normal conditions. *J. Biol. Chem.* **19**: 1-24, 1914.
21. Avery, J. F., and Paulley, J. W. Intestinal lipodystrophy (Whipple's disease). *Lancet* **1**:214-216, 1949.
22. Ingle, D. J. Relationship of adrenal cortex to metabolism of fat. *J. Clin. Endocrinol.* **3**:603-612, 1943.
23. Barnes, R. H., Rusoff, I. I., and Burr, G. O. Adrenalectomy and absorption of different fats. *Proc. Soc. Exper. Biol. & Med.* **49**: 84-87, 1942.
24. Bavetta, L. A. Effect of adrenalectomy on absorption of short chain fatty acids and their triglycerides. *Am. J. Physiol.* **140**:44-46, 1943.
25. Stillman, N., Entenman, E., Anderson, E., and Chaikoff, I. L. Phosphorylation of fat in absence of adrenal glands as measured with radioactive phosphorus. *Endocrinology* **31**:481-485, 1942.
26. Sailer, S., and McGann, R. J. Lipophagic granulomatosis of enteric tract. *Am. J. Digest. Dis.* **9**:55-63, 1942.
27. de Groot, A. L. Oorspronkelijke stukken: over een endocrine stoornis met verschijnselen van inheemsche spruw en van de ziekte van Addison. *Nederl. tijdschr. v. geneesk.* **90**:720-724, 1946.
28. Bergner, G. E., Lewis, R. A., Stout, F. W., Thorn, G. W., and Emerson, K., Jr. Effect of 11-dehydrocorticosterone on fecal fat excretion. *J. Clin. Endocrinol.* **8**:606, 1948.
29. Pemberton, J. deJ., Comfort, M. W., Fair, E., and Zaslow, J. Intestinal lipodystrophy (Whipple's disease): preliminary report of three cases in early stage of disease. *Surg., Gynec., & Obst.* **85**: 85-91, 1947.

PSEUDOPRECOCIOUS PUBERTY IN GIRLS AS A RESULT OF ESTROGEN INGESTION*

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THE purpose of this paper is to report 2 cases of precocious secondary sexual development resulting from the ingestion of estrogenic substances by young girls, to point out the clinical peculiarities of this type of sexual precocity and to emphasize the importance of including estrogen ingestion in the differential diagnosis of pseudopuberty in females.

CASE REPORTS

CASE 1. A 4-3/12-year-old girl was referred to the hospital because of tenderness and enlargement of both breasts, together with dark pigmentation of the areolae, of 3 weeks' duration. Two days before admission scanty vaginal bleeding had occurred.

The family history was noncontributory; there was no record of the occurrence of early puberty in close female relatives. The past history indicated normal growth and development until the occurrence of the breast changes. The mother, a registered nurse, denied any possibility of the child's having been exposed to estrogenic substances.

Physical examination revealed a healthy-appearing child in the 30th percentile for height and weight. The breasts were developed to the primary mamma stage, with definite glandular tissue palpable bilaterally. Both the nipples and areolae were darkly pigmented. Axillary hair was absent, but a scanty growth of downy hair was visible on the mons pubis. The cervix was visualized with the aid of a nasal speculum and was found to be slightly larger than the normal for the patient's age. On rectoabdominal examination the body of the uterus could not be made out, but a firm fixed mass was palpable in the left vault.

X-ray examination of the skull, chest and abdomen was negative and the bone age was normal. A test for follicle-stimulating hormone[1] was negative for 6.5 units. The 11-oxysteroids[2] were 0.1 mg. and 17-ketosteroids[3] 0.22 and 0.37 mg. per 24 hours. The vaginal pH was acid, and the vaginal smear contained many precornified cells, indicative of moderate estrogen stimulation. Chemical assay of the urine for natural estrogens[4] showed less than 1 gamma, a surprising finding in view of the physical manifestations of estrogen stimulation.

A preoperative diagnosis of a solid tumor of the left ovary (question of granulosa-cell tumor) was made, and an exploratory laparotomy performed. The uterus and fallopian tubes proved to be enlarged and hyperemic, but no abnormal masses were found. The uterus was tilted to the left, and it was clear that the mass that had been felt in the left adnexa was, in reality, the fundus of the uterus. Bilateral ovarian biopsies were taken after inspection showed the ovaries to be firm, equal in size, and grossly normal.

Histologic studies of the biopsy material showed normal preadolescent ovarian tissue, with no evidence of follicular activity.

After the laparotomy further questioning brought out the fact that stilbestrol had been in the house and easily available to the child, the mother having taken the drug until 4 months before the appearance of the child's precocious breast development. Actual ingestion by the child was never definitely proved.

Follow-up examination 1 month postoperatively showed complete regression of the breast enlargement and a considerable decrease in the pigmentation (Fig. 1). No further vaginal bleeding had occurred, and on rectal palpation it was apparent that the uterus and cervix had regressed to normal dimensions.

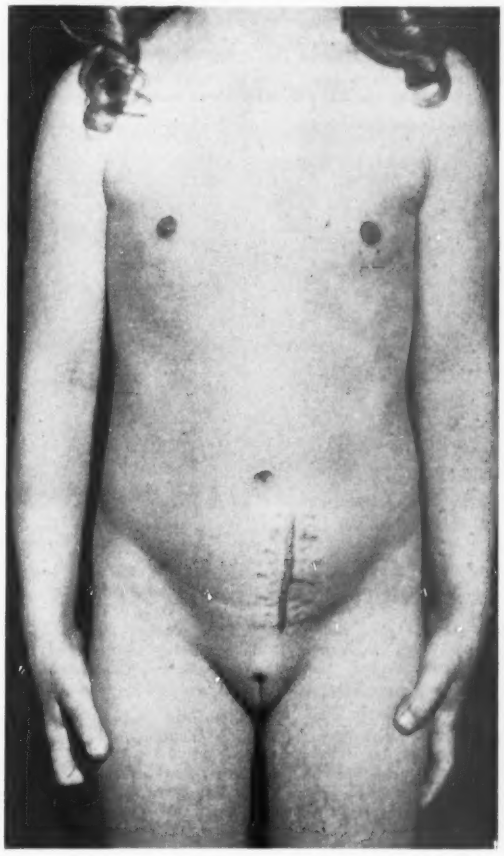

FIGURE 1. *Appearance of the Patient in Case 1 a Month after Laparotomy, Showing the Residual Areolar Pigmentation and the Healed Laparotomy Wound.*

Two years after operation physical examination demonstrated an entirely normal child without signs of secondary sexual development or areolar pigmentation. The pubic hair was preadolescent in character, and the external genitalia were normal. She was in the 40th percentile for height and weight.

CASE 2. A 7-year-old girl was referred to the Children's Medical Center because of bilateral breast enlargement of 4 weeks' duration and vaginal bleeding that had begun 3 days before admission and required the wearing of 1 napkin

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Aided by a grant from the Commonwealth Fund of New York to the Children's Medical Service, Massachusetts General Hospital.

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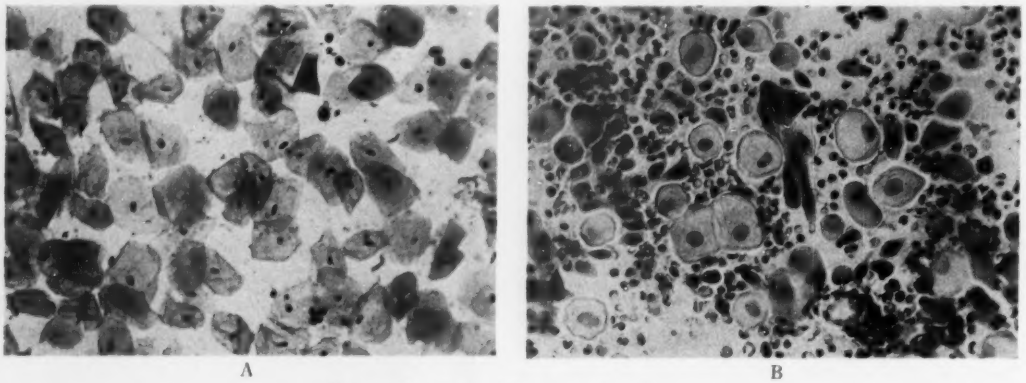
a day. Further investigation revealed that the child, who attended a boarding school, was taking4 pills 3 times a day from a single bottle containing 7 different types of medication, all supposedly vitamin preparations given to her by her physician-father. Approximately 6 days after leaving boarding school and returning home because of the breast changes, the patient began to have vaginal bleeding; during this period no medication had been taken.

Physical examination revealed an intelligent child who was in the 10th percentile for height and weight. The most striking external finding was early breast development, glandular tissue being readily palpable beneath the areolae, with intense brownish-black pigmentation of the nipples and areolae. There was also pigmentation of the axillary and inguinal folds, linea alba and external genitalia. Palpation of the abdomen was negative, but rectal examination demonstrated the uterus and cervix to be enlarged to 2 or 3 times the normal size for the child's age. There was minimal vaginal bleeding on admission, but this ceased after 24 hours.

X-ray examination of the skull, chest and abdomen was negative. All laboratory findings were within normal limits except for the vaginal pH, which was acid, the vaginal smear (Fig. 2*A*), which contained many cornified and precornified cells, indicating marked estrogenic stimulation, and the urinary gonadotropin assay, which was positive for 3.3 mouse units[4] (the only dilution run).

Bioassay of the suspicious tablets, the only white pills that the child had been taking, was carried out by their administration to female rats. The presence of estrogenic activity in the tablets was demonstrated by the induction of marked uterine enlargement in the test animals. Further inquiry at this point established beyond question the fact that the patient's father had mistakenly given her stilbestrol instead of ascorbic acid tablets. She had received approximately 2 mg. of stilbestrol daily for 4 weeks. The child was therefore discharged and re-examined 2 months later. By this time the breast tissue was no longer palpable and the pigmentation had decreased considerably in intensity. There had been no further vaginal bleeding. A vaginal smear (Fig. 2*B*) contained only basal cells, indicating an absence of estrogenic stimulation. A second gonadotropin assay was negative for 3.3 mouse units. Four months after discharge the breasts had again become juvenile in every respect.



A B

FIGURE 2. *Vaginal Smears in Case 2.*

A = *smear taken ten days after discontinuance of stilbestrol, showing marked estrogen effect. Sixty-four per cent of the cells are cornified, and no cells from the basal layer of the vaginal epithelium are seen. There is a complete absence of leukocytes.*

B = *smear taken two months after discontinuance of stilbestrol, showing no estrogen effect. A great many leukocytes are present. The majority of the epithelial cells are inner-layer basal cells, with only an occasional outer-layer basal cell. There are no cells of the superficial layer (Papanicolaou stain, X210).*

DISCUSSION

The patients described above both presented with breast enlargement, with intense brownish-black pigmentation of the areolae, nipples and linea alba and with vaginal bleeding. In both cases the vaginal pH was acid, and the vaginal smear indicated that estrogenic stimulation of the vaginal epithelium had occurred. Except for the positive gonadotropin assay in Case 2, the laboratory findings were within normal limits.

In Case 1 the history of the presence of stilbestrol in the house, the character of the operative findings and the rapidity of the subsequent sexual regression are believed to constitute strong circumstantial evidence of the occurrence of estrogen intoxication. Exploratory laparotomy revealed nothing except hypertrophy of the fallopian tubes and uterus.

In Case 2 a history of stilbestrol ingestion was obtained in time to avert a laparotomy. Even without the aid of the subsequent history and the biossay of the unknown tablets, a period of two to four weeks' observation could have suggested the correct diagnosis because such an interval suffices to permit regression of the stimulated vaginal epithelium and cessation of uterine bleeding.

Because sexual abnormalities in children are a source of grave concern to parents, the premature appearance of secondary sexual characteristics generally results in prompt consultation with a physician. Every diagnostic aid is thereupon utilized, and even such drastic procedures as pneumoencephalography and exploratory laparotomy are often considered necessary to exclude organic lesions of the brain and ovary. The hasty employment of such radical diagnostic measures reflects

a lack of familiarity with the actual incidence of the various causes of sexual precocity. Thus, constitutional "idiopathic" precocity is believed to account for 80 to 90 per cent of all cases of sexual precocity in girls.[5] Lesions of the ovary, together with polyostotic fibrous dysplasia, account for most of the few remaining cases. Despite the comparative rarity of ovarian cysts and tumors as a cause of female precocity, laparotomy is sometimes resorted to even in the absence of a palpable tumor, as nearly occurred in Case 2. The argument advanced in justification of such a procedure is that an ovarian lesion too small to be palpable may be present and that such a lesion, if malignant, may be susceptible to cure by immediate surgical excision. However, data from the pathological and surgical files of the Children's Hospital[6] and the Massachusetts General Hospital[7] indicate that granulosa-cell tumors are rarely malignant in the early, nonpalpable stage. The course of the patients discussed above therefore suggests that it may be sound clinical procedure to institute a period of two to four weeks' observation before laparotomy is even considered in patients in whom careful physical examination reveals no definite evidence of a pelvic tumor.

The importance of entertaining the possibility of ingestion of estrogens or exposure to these substances, even in the face of a negative history, is also clear from the histories of these patients. If vaginal bleeding has not already taken place in a child rendered precocious by estrogen, this may occur after withdrawal of the hormone. Objective changes of great diagnostic value will, in addition, be found in the vaginal mucosa if sought for by means of serial studies of the vaginal smear. According to Shorr,[8] the effect of estrogen on the vaginal epithelium will disappear within fourteen to twenty-one days of cessation of oral medication; MacBryde[9] gives twenty-one to thirty days as the time required for complete regression after full stimulation has been produced by stilbestrol.

Since stimulation by estrogenic substances may follow inhalation and absorption through the skin as well as ingestion, all possible means of contact must be explored in obtaining the history. The four-year-old boy with gynecomastia and pigmentation described by Prouty[10] was merely exposed for "several weeks" to the clothing worn by his mother during her work as a packer of stilbestrol tablets. The same child had a ten-year-old sister who simultaneously manifested breast enlargement, areolar pigmentation and vaginal bleeding, the last two signs disappearing when exposure to the stilbestrol-impregnated clothing was terminated. Hesselvik[11] described a ten-month-old boy with similar changes caused by percutaneous absorption of stilbestrol from a hand ointment used by his mother for eczema. An exposure of only "several weeks" produced the findings. Another case seen by one of us was that of a preadolescent girl in whom striking pigmentation of the nipples and areolae (Fig. 3) followed attempts to induce breast development by the local application of stilbestrol ointment.

The physical finding particularly suggestive of exogenous estrogens as a cause of pseudoprecocity in females is the intense, dark-brown pigmentation of the areolae of the breasts. Indeed, it was the prominence of the pigmentation in Case 2 that led to a delay in performance of laparotomy while further inquiries were made. Similar pigmentation has long been noted in adults of both sexes to whom large quantities of stilbestrol have been administered for therapeutic purposes.[12] Such pronounced pigmentary changes are not usually seen in other forms of precocity. The pathogenesis of the pigmentation is not well understood although its similarity to the chloasma of pregnancy has been pointed out. In a series of experiments in vitro Figge[13] has shown that the inhibitory effect of glutathione on melanin formation can be neutralized by estrone. This reaction may occur in vivo as well.

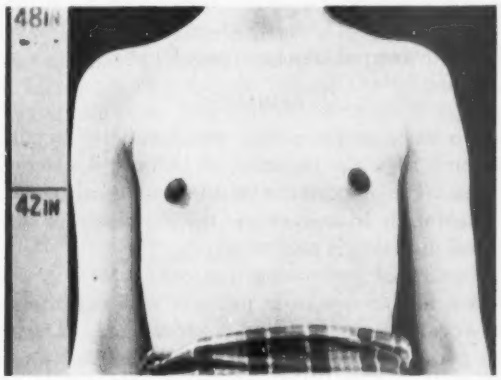


FIGURE 3. *Pigmentation of the Nipples and Areolae in a Preadolescent Girl, Resulting from the Local Application of Stilbesterol Ointment.*

It should be pointed out that the absence of pigmentation does not exclude the possibility of precocity from estrogen ingestion since, at least in the amounts used therapeutically in children, estrone sulfate appears to be less potent than stilbestrol in inducing pigmentation. That such naturally occurring estrogens can induce pigmentation has been demonstrated experimentally,[14] but there does not appear to be a simple, direct correlation between estrogenic potency and the capacity to induce pigmentation.[15]

The demonstration of the presence of gonadotropic hormone in the urine shortly after ingestion of stilbestrol had ceased in Case 2 is of both theo-

retical and practical interest. Although the protracted administration of large doses of estrogens to animals appears to result in suppression of pituitary gonadotropin secretion, the administration of short courses or small doses of estrogen may actually stimulate gonadotropin release.[16] Brown and Bradbury[17] have extended this work to the human female, and have shown that the administration of a single large dose of stilbestrol results in the excretion of abnormally large amounts of gonadotropin in the urine. It is possible that in Case 2 a similar stimulation of the pituitary occurred. The disappearance of measurable gonadotropin from the urine two months later lends support to this hypothesis. If this finding is confirmed, gonadotropin assays may prove to be less reliable than was formerly thought in the differentiation of true puberty from pseudopuberty.

Summary

Two cases of precocious pseudopuberty in girls resulting from the ingestion of stilbestrol are presented. The importance of the finding of areolar pigmentation in suggesting the diagnosis of stilbestrol ingestion is pointed out.

A policy of postponing laparotomy for a period of two to four weeks in patients with negative or equivocal pelvic findings is advocated. During this period regressive changes in the vaginal smear provide material aid in establishing the diagnosis of medicational precocity.

The theoretical implications of the positive assay for gonadotropin in the urine of one of the patients are discussed.

We are indebted to Dr. Nathan B. Talbot for permission to report Case 1, to Mrs. Ruth Graham for the interpretation of the vaginal smear and to Mr. John Carabitses for the photomicrographs.

References

1. Klinefelter, H. F., Albright, F., and Griswold, G. C. Experience with quantitative test for normal or decreased amounts of follicle stimulating hormone in urine in endocrinological diagnosis. *J. Clin. Endocrinol.* **3**:529-544, 1943.
2. Talbot, N. B., Saltzman, A. H., Wixom, R. L., and Wolfe, J. K. Colorimetric assay of urinary corticosteroid-like substances. *J. Biol. Chem.* **160**:535-546, 1945.
3. Talbot, N. B., Berman, R. A., MacLachlan, E. A., and Wolfe, J. K. Colorimetric determination of neutral steroids (hormones) in 24-hour sample of human urine (pregnandiol: total, alpha and beta alcoholic, and nonalcoholic 17-ketosteroids). *J. Clin. Endocrinol.* **1**: 668-673, 1941.
4. Engel, L. L., Slaunwhite, W. R., Carter, P., and Nathanson, I. T. Separation of natural estrogens by counter-current distribution. *J. Biol. Chem.* **185**:255-263, 1950.
5. Novak, E. Constitutional type of female precocious puberty with report of 9 cases. *Am. J. Obst. & Gynec.* **47**:20-42, 1944.
6. Gross, R. E. Personal communication.
7. Castleman, B. Personal communication.
8. Shorr, E. Personal communication.
9. MacBryde, C. M., Freedman, H., Loeffel, E., and Castrodale, D. Synthetic estrogen stilbestrol: clinical and experimental studies. *J. A. M. A.* **115**:440-443, 1940.
10. Prouty, M. Gynecomastia with pigmentation in four year old male following stilbestrol exposure. *Pediatrics* **9**:55-57, 1952.
11. Hesselvik, L. Signs of sexual precocity in male infant due to estrogenic ointment. *Acta paediat.* **41**:177-185, 1952.
12. Nathanson, I. T., and Kelley, R. M. Hormonal treatment of cancer. *New Eng. J. Med.* **246**:135-145 and 180-189, 1952.
13. Figge, F. H. J., and Allen, E. Release of glutathione inhibition of melanin formation by estrone. *Endocrinology* **29**:262-266, 1941.
14. Davis, M. E., Boynton, M. W., Ferguson, J. H., and Rothman, S. Studies on pigmentation of endocrine origin. *J. Clin. Endocrinol.* **5**:138-146, 1945.
15. Nathanson, I. T. Personal communication.
16. Lane, C. E. Some influences of oestrin on hypophyseal-gonad complex of immature female rat. *Am. J. Physiol.* **110**:681-685, 1935.
17. Brown, W. B., and Bradbury, J. T. Estrogen release of pituitary gonadotropin in women. *Tr. Am. Soc. Study Sterility* **3**:117-124, 1947.

PROBLEMS AND PRACTICES IN A COMMUNITY HOSPITAL*

II. Postoperative Stricture of the Biliary Tract

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THIS paper reviews common-bile-duct injuries treated at the Henry Heywood Memorial, a 120-bed hospital,[1] from January 1, 1941, through December 31, 1950, during which there were 539 consecutive operations on the gall bladder or biliary tree, with 4 cases of loss of continuity of the biliary tract. In a review of our experience with gall-bladder surgery, it was disturbing to find that in each of 4 cases, a patient entered the hospital with biliary disease that appeared to be a straightforward problem, only to go through a long period of additional surgical procedures crippling to his health, morale and financial status.

That the postoperative complication of disturbed continuity of the biliary tract is not rare is evidenced by reports from large clinics and experience based on secondary procedures necessitated because of injury to the common or hepatic ducts during "routine" cholecystectomy. The number of such operations is impressive. At the Mayo Clinic, Walters and Cameron[2] operated on 27 patients for stricture of the bile duct in 1948 alone, with a total of 184 cases from 1924 through 1948. From the Illinois Research Hospital, Cole and his associates[3] reported 108 operations on 92 patients with strictures of the common duct during a thirteen-year period ending in 1950; from the Presbyterian Hospital, New York City, Whipple et al.[4] described similar operations on 54 patients from 1936 to June, 1949. Although operative trauma was not responsible for all the strictures, it accounted for a large percentage of the cases.

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Some idea of the extent of bile-duct injuries in New England may be obtained from successive papers from the Lahey Clinic. A report by Lahey and Pyrtek[5] in 1950 covered 280 strictures of the bile duct, and one by Lahey[6] the following year gave 314 cases to date. Commenting on the large number of patients operated on for bile-duct stricture, Lahey, in the course of a discussion of a paper by Massie,[7] made the following significant statement:

> This is a serious criticism of surgery. If we have operated on that number of patients with duct injuries how many others have died? How many others have been operated on by other surgeons? Think of how many gallbladder operations are performed daily, and that every cholecystectomy exposes the patient to this hazard. We have to realize that every one of these patients who has a safe removal of the gallbladder is well, that every one with an injury to the bile ducts is an invalid, and that every procedure you employ after that is a makeshift one.

Although many of the patients with bile-duct injury treated in the larger clinics have been referred from smaller hospitals, analyses of the causes of the injuries necessitating such repair operations rarely emanate from these primary sources. This probably results, in part, from reluctance to report such surgical tragedies by those who have played some role in their occurrence. Also, from our experience, we are convinced that most of these cases are buried in hospital record rooms by inadequate final diagnoses. In our files, not 1 of the 4 cases reported below was diagnosed as stricture of the bile duct. This did not represent deception on the part of the physician since the final diagnosis was not proved until the secondary operation at another hospital, and the corrected final diagnosis did not appear in our records. Under the present record system such diagnoses rarely get back to the original hospital unless specifically requested. Our cases were discovered only by a reading of the individual case histories and follow-up examination in all suspicious cases. Our attention was first called to the problem when Case 4 came up in a staff discussion. The surgeon in Case 3 was still a member of the staff and recalled his case of the previous year. Cases 1 and 2, however, were not found until we discovered them in the study of the records, noted the typical course and did the follow-up examination. Therefore, no one should make the statement that bile-duct injuries have never occurred in his hospital without having made a similar type of survey. We consider our record room to be well organized and of high standard, and yet, on the basis of the cross-index files alone, we too could have claimed complete immunity from this complication.

Our hospital statistics show a constant upward trend in the number of patients treated for surgical diseases of the biliary tract (Table 1), and it is reasonable to assume that in the future a large proportion of such patients will be treated in community hospitals such as ours. We believe, therefore, that cases of bile-duct injury should be reviewed critically at the primary level, and that our effort should be directed toward the prevention of the injury or, that failing, toward the proper handling of the case. The prevention of these injuries is the single factor of greatest importance, and yet preventive measures have been analyzed largely by those who have had the doubtful privilege of doing secondary operations to repair the biliary system. This paper is an attempt to report the problem close to the source and to re-emphasize it at this level.

TABLE 1. *Biliary-Tract Surgery at Henry Heywood Memorial Hospital (1941–1950).**

TYPE OF CASE	ENTIRE PERIOD		FIRST FIVE YEARS		SECOND FIVE YEARS	
	TOTAL	PERCENTAGE	TOTAL	PERCENTAGE	TOTAL	PERCENTAGE
Gall-bladder operations	539		210		329	
Cholecystectomies	435	80.7	155	73.8	280	85.1
Cholecystostomies	96	17.3	54	25.7	42	12.8
Choledochotomies	51	9.5	9	4.3	42	12.8
Deaths	17	3.2	12	5.7	5	1.5
Loss of continuity of bile duct	4	0.7	3	1.4	1	0.3
Traumatic stricture	3	0.5	2	0.9	1	0.3
Inflammatory obliteration	1	0.2	1	0.5	0	

*One evaluation of the trend in surgical procedures is the percentage distribution of the various types of operation in the two five-year periods. These figures show an increase in cholecystectomies, a 50 per cent decrease in cholecystostomies and a great increase in choledochotomies. That the number of cases in which the common bile duct is explored is continuing to increase is shown by the values of 4.3 and 12.8 per cent in the successive five-year periods, and also by the fact that in the final year of the survey choledochotomy was done in 26 per cent of the cases. During the years 1951 and 1952, figures for which are not included in this survey, choledochotomies increased to 29 and 33 per cent, respectively, and cholecystostomies decreased to 12 and 6 per cent, respectively.

To picture this hospital's surgical experience with biliary-tract disease pertinent data on the 539 patients operated on during the ten years under review (Tables 1 and 2) are divided, for purposes of comparison and discussion, into two consecutive five-year periods. No attempt is made to analyze these figures. A few points in the general picture are noted, however, as an indication that our practices and experience are similar to those of other hospitals.

To assure ourselves that we had not missed any case, we made a list of the patients on whom each surgeon had operated. These lists were distributed to the various surgeons concerned, who were requested specifically to check from their personal

files whether jaundice had developed after any of these patients left the hospital, and whether they had been admitted to another hospital because of further symptoms of biliary disease. In a community of this character, where patients are known more intimately than in a large city, such a follow-up study proves most satisfactory. Jaundice does not develop in areas such as those we serve without its being well known and a topic of general conversation among the public. In this way, we were able to obtain accurate follow-up results in 95 per cent of the cases. As noted above, it was only through this means that we discovered 2 of the cases of bile-duct injury.

Postoperative Strictures of the Biliary Tract

The 4 cases of loss of continuity of the biliary tract occurring during the ten years of our study represent an incidence of 0.74 per cent among all the biliary-tract operations; for the two consecutive five-year periods the figures are 1.4 and 0.3 per cent respectively. The last case was reported in March, 1946. This complication has not occurred during the succeeding six years, in which there have been, 455 consecutive operations on the biliary tract. Although we had no acceptable statistics for comparison, it was our certain belief that our over-all figure of less than 1 per cent of cases with loss of continuity of the biliary tract during the ten years under review was too high and warranted careful study of the individual cases.

Table 2. *Mortality in Biliary-Tract Surgery.**

Period	No. of Operations	No. of Deaths	Mortality	Causes of Death			
				Coronary occlusion	Hemiplegia	Pulmonary embolism	Postoperative hemorrhage
			%				
Entire ten years	539	17	3.2	5	1	3	1
First five years	210	12	5.7	3	1	2	1
Second five years	329	5	1.5	2	0	1	0

*To eliminate individual interpretations of cause of death, mortality figures include every death occurring during the postoperative hospital stay, regardless of cause. Mortality statistics do not give the entire picture but are a reasonable index of the surgical experience of a hospital. The operations were performed by different members of the surgical staff.

†Exact cause of death questionable — autopsy not performed, and clinical record somewhat obscure.

Case Reports

Case 1. M. H. (H.H.M.H. 52125), a 33-year-old woman, had undergone an apparently uncomplicated cholecystectomy on February 1, 1943. Poorly controlled shoulder-girdle pain developed on the 3d day, followed by fever, vomiting and a copious discharge of bile from the wound on the 4th day. The stools were acholic; the patient became jaundiced, and a chronic bile-discharging sinus developed. On February 21 a 2d operation was attempted but was abandoned because of the poor condition of the patient. At a 3d operation, performed on April 20, the head of the pancreas was described as being hard and nodular, and 2 lymph nodes were removed, later being reported as hyperplastic. There was no report that the common duct was exposed. The patient was discharged on May 11 (the 111th postoperative day), with a diagnosis of pancreatitis, cholelithiasis and cholecystitis. Three and a half months later, she was readmitted with symptoms of increasing biliary obstruction, and was transferred to a Boston hospital, where a stricture of the common duct was found, and a plastic repair accomplished. From that date until 1949, she had 6 further plastic procedures. She still has periodic attacks of pain, chills and fever — but without their former severity.

The record in this case showed many operations during a six-year period after the original cholecystectomy. It appears that this chain of events was initiated by the original operation, and that the most likely precipitating factor was an injury to the common duct. The pancreatitis found at the third operation was undoubtedly secondary to the accompanying bile peritonitis. Although this inflammatory process may have added fuel to the fire, it was not the original spark. There was no note, at the time of the first operation, of any technical difficulty or possibility of injury. There is therefore no way of explaining how the loss of continuity of the duct occurred. However, if one postulates that when the cystic duct was put on traction, the suture or clamp included all, or a portion, of the common duct, the subsequent course is easily explained.

This case illustrates three generalizations, which, for emphasis, should be mentioned here: one should beware of the "easy" gall bladder; with evidence of biliary obstruction not apparent preoperatively or at the time of operation, an injury to the biliary tract must be assumed until the contrary is proved; and subsequent operations should not be undertaken without consultation with a surgeon skilled and widely experienced in the repair of biliary-tract injuries.

Case 2. F. C. (H.H.M.H. 54585), a 40-year-old woman, underwent a cholecystectomy, without apparent technical difficulty, on October 23, 1943. She was discharged from the hospital on November 6, being readmitted on January 4, 1944, complaining of right-upper-quadrant pain, itching, jaundice and acholic stools of 2 months' duration.

At operation the common duct was found and opened, and a T tube inserted (this did not drain bile at any time). The patient improved clinically and was discharged on February 15. She remained well until September, when she again had itching jaundice and acholic stools until 1 year later. This cleared and was followed by a year of comparative well-being. In November, 1946, she again became jaundiced and was admitted to the hospital and later transferred to a Boston hospital. On February 14, 1947, she was

operated on, and the surgeon was able to identify only the lower end of the common duct. The liver showed biliary cirrhosis and evidence of former abscess formation. The patient died on the following day. At autopsy the right hepatic duct was found in the liver substance, but no sign of ducts was found in the cleft.

From the records of this case, it appears that infection may have been the major cause of the loss of continuity of the bile ducts.[8-10] Evidence of infection was found at the secondary operations, and there were periods, one of a year's duration, when the patient was quite free of symptoms of biliary obstruction. No fistula was ever demonstrated to account for this, as has been noted occasionally.[8] Certainly, there would not have been such long periods of freedom of symptoms if there had been complete mechanical obstruction. The history of the case is consistent with partial obstruction or stricture, with infection, as a cause of symptoms.[3]

Table 2 (*Concluded*).

Period	Causes of Death					
	Epilepsy and postoperative hemorrhage	Circulatory collapse (cyanosis)†	Bile peritonitis from preoperative gall-bladder rupture	Bile peritonitis from pulling out of tube	"Liver death"†	Carcinoma of gall bladder (inanition)
Entire ten years	1	1	2	1	1	1
First five years	1	1	1	0	1	1
Second five years	0	0	1	1	0	0

Case 3. M.H. (H.H.M.H. 58828), a 26-year-old woman, was subjected to a cholecystectomy on February 3, 1945. The surgeon noted that exposure and dissection were difficult. On the 9th day after operation a tender mass, which discharged, spontaneously, large amounts of bile, developed. The possibility of bile-duct injury was recognized and transfer to a surgeon with greater experience in the operative treatment of this complication was arranged. The patient was explored, and a stricture of the common duct found and repaired, with complete recovery of the patient. She has been well since that time.

We believe that this case illustrates the proper course to follow once such an injury has occurred. Although the surgeon did not recognize, at the time of operation, that he had injured the common duct, he did make the diagnosis promptly when the postoperative course of the patient became apparent. He at once consulted a surgeon experienced in treating injuries of the biliary tract. As a result, this patient had only one secondary operation, followed by excellent postoperative recovery, in contrast to Case 1, in which the nature of similar symptoms appearing at about the same interval after the original operation was not appreciated.

Case 4. C.M. (H.H.M.H. 63537), a 60-year-old woman, had a cholecystectomy, without recorded technical difficulty, on March 5, 1946. Jaundice was noted on the 4th day, and on the 18th day, a bulging mass of the wound was incised, with the discharge of 760 cc. of clear bile. The wound continued to discharge bile, and on May 18, a 2d operation was attempted. At this time, the surgeon reported a penetrating ulcer on the lesser curvature of the stomach in the prepyloric area, with edema about the common duct. He further reported that the common duct was probed and then a small catheter was passed. The patient was discharged on June 11. Ninety-eight days after admission, on November 14, she was admitted to a Boston hospital, with jaundice, itching and acholic stools of 2½ months' duration. At operation, the common duct was found completely obstructed for a distance of 1 cm. A plastic repair was accomplished, and she was discharged on December 23. At present, she is doing well.

This case, in many ways, parallels Case 1. In both cases, trouble first became evident by the fourth postoperative day. Exploratory operations were done over two months later, and the patients were discharged within a month, only to be hospitalized again three and a half to five months later with the diagnosis of common-duct injury and subsequent corrective surgery. The comments noted under Case 1 are equally applicable here.

Discussion

In Case 2 there seems to be no question that an inflammatory process was largely responsible for the loss of continuity of the common duct, although there may have been partial obstruction as well. In the other cases, the histories and findings at subsequent operations are most typical of traumatic injury to the duct. These cases are differentiated from Case 2 by the fact that the first evidence of trouble appeared as early as the third, fourth or fifth postoperative day, whereas in Case 2, no symptoms were noted until about two weeks after discharge from the hospital. Attention might also be called again to the observation of Graham[10] that the most significant differentiation between traumatic and inflammatory stricture is obliteration of the bile duct, even into the liver in the inflammatory form. This was a finding only in Case 2 of the present series. The surgeon who regards inflammatory obliteration as explaining *all* cases of bile-duct stricture will find, only too often, that it is of questionable value. Certainly, the assumption that such injuries as become evident within three to five days of operation are all traumatic engenders a far healthier approach to the problem.

Perhaps the most important point in the comparison of these 4 cases of loss of continuity of the biliary tract was the surgeon's prompt realization (in Case 3 alone) of the probable cause of the

difficulty that developed a few days after a presumably uncomplicated operation and his immediate referral of the case to a surgeon with greater experience in the treatment of such injuries.

It is now six years since the last common-duct injury occurred in this hospital. At that time, the surgical staff had several meetings at which the problems of gall-bladder disease were discussed. These discussions were based mainly on our own experience. As we look back on this study, the single factor of greatest importance in promoting better biliary-tract surgery appears to be frank discussion of these cases, which time and inadequate diagnoses can completely hide in the record room. A study of such cases forces any surgeon to approach a gall-bladder operation with intelligent caution and awareness of the importance of careful operating, even in the "easy" gall bladder. One might believe that duct injuries are most prone to occur in the difficult operations. Our study does not bear this out since, as nearly as can be determined, at least 2 of the cases were straightforward operations without technical difficulty. Although poorly controlled hemorrhage with resultant blind clamping of the cystic vessel is listed as a common cause of bile-duct injury, it was not a factor in any of these cases. There has been no case of duct injury in any of our choledochotomies, which precludes a careful identification of the duct structures. Careful and proper dissection sufficient to identify accurately the cystic duct, cystic artery and common duct would prevent most, if not all, duct injuries.

In the actual performance of the operation, certain precepts should be kept in mind:

There is a high incidence of congenital anomalies of the biliary system.[11,12]

The surgeon should familiarize himself early in the operation with the exact location of the structures of the gastrohepatic ligament so that untoward bleeding from the cystic artery may be safely controlled, by pressure of the hepatic artery between the thumb and forefinger, obviating the hasty, blind application of clamps.

A primary task of the surgeon is to demonstrate, anatomically, the cystic artery and duct before removal of the gall bladder is considered.

The angle between the cystic duct and the common duct should be well exposed. (This we believe to be of great importance.)

The cystic artery should be exposed to its entrance to the gall bladder and tied close to this point.

It is safer to tie the cystic duct before clamping, and the clamp should be distal to the well visualized tie.

One should beware of applying ties or clamps while traction is applied to the gall bladder. The duct system with lax peritoneal investments is the one that is easily knuckled. (In Cases 1 and 4 this may have been the cause of the injury.)

In acute cases, if the landmarks are obliterated by marked edema, a cholecystostomy may be the operation of choice. Secondary removal of the gall bladder is a far less formidable procedure than repair of the injured ductal system.

There are no "easy" cholecystectomies. A speedy operation may be a dangerous one.

It makes little difference which technic is used in a cholecystectomy so long as the surgeon can identify each duct structure and can assure himself that he will be master of any untoward bleeding that may occur.

These statements are not original, similar ones having appeared in the world medical literature. Prevention of injury to the ducts by close adherence to these well known precepts should be the primary object of every surgeon undertaking gall-bladder surgery. At the end of a cholecystectomy the bile ducts should be carefully inspected, and if the surgeon finds that injury has occurred, he should repair it immediately. Any surgeon who undertakes the responsibility of a gall-bladder operation should be ready to carry out this technical procedure. This is the time at which repair is easiest and can be done with the least difficulty.[13]

If it becomes apparent early in the postoperative period that a previously unrecognized injury has occurred, we believe that a surgeon widely experienced in plastic repair on the biliary tract should be consulted at once. The surgeon undertaking the repair should not be forced to face a most difficult operation further complicated by the increased scar tissue of previous unsuccessful secondary operations.

Summary

Four cases of loss of continuity of the common bile duct after cholecystectomy are reported, at least 3 of which are attributable to bile-duct injury from surgical trauma. From the lessons learned, certain precepts designed to prevent further repetition of this complication are stated. A course of action that seems proper for a community hospital if injury to the bile duct is found postoperatively is recommended.

There have been no bile-duct injuries at the Henry Heywood Memorial Hospital during the past six years, during which we have performed 455 consecutive operations on the biliary tract.

References

1. Pierce, F. R., and Domenici, T. J. Problems and practices in community hospital. I. Treatment of venous thrombosis. *New Eng. J. Med.* **242**:395-402, 1950.
2. Walters, W., and Cameron, J. M. Studies of biliary strictures and their surgical treatment in 184 patients. *Proc. Staff Meet., Mayo Clin.* **25**:150-156, 1950.
3. Cole, W. H., Ireneus, C., and Reynolds, J. T. Strictures of common duct. *Ann. Surg.* **133**:684-696, 1951.
4. O'Malley, R. D., Aufses, A. H., Jr., and Whipple, A. O. Benign extrahepatic biliary tract obstruction: analysis of 54 cases. *Ann. Surg.* **134**:797-807, 1951.

5. Lahey, F. H., and Pyrtek, L. J. Experience with operative management of 280 strictures of bile ducts with description of new method and complete follow-up study of end results in 229 cases. *Surg., Gynec. & Obst.* **91**:25-56, 1950.

6. Lahey, F. H. Split T tube and retaining apparatus for indwelling T tubes in repair of strictures of bile duct. *Surg., Gynec. & Obst.* **93**:173-176, 1951.

7. Massie, F. M. Longmire operation for common duct obstruction. *Ann. Surg.* **131**:838-845, 1950.

8. Cattell, R. B. Causes of unsatisfactory results after operation on gallbladder and bile ducts. *Postgrad. Med.* **7**:351-356, 1950.

9. Flickinger, F. M., and Masson, J. C. Reconstructive operations for benign stricture of bile ducts. *Surg., Gynec. & Obst.* **83**:24-36, 1946.

10. Graham, H. F. Inflammatory obliteration of common and hepatic ducts following cholecystectomy. *Ann. Surg.* **126**:811-813, 1947.

11. Cole, W. H. Congenital anomalies of bile duct and adjacent blood vessels. *Surg., Gynec. & Obst.* **87**:111, 1948.

12. Johnston, E. V., and Anson, B. J. Variations in formation and vascular relationships of bile ducts. *Surg., Gynec. & Obst.* **94**:669-686, 1952.

13. Lahey, F. H. Technic of repair of strictures of bile duct. *S. Clin. North America* **31**:719-734, 1951.

THE ROLE OF CORTISONE IN THE TREATMENT OF SEVERE BRONCHIAL ASTHMA*

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CORTISONE has become increasingly available for therapy, and many investigators[1-10] have reported its dramatic role in the relief of asthmatic attacks; yet the mechanism by which it relieves symptoms is still unknown. All are now in agreement that asthma returns once cortisone therapy is stopped, and the proper management of bronchial asthma, therefore, still must be primarily concerned with an attempt to make an etiologic diagnosis. This study considers the selection of appropriate cases for the administration of cortisone and optimal dosage levels.

SELECTION OF CASES

We have found cortisone useful in the following types of severe asthma: patients with status asthmaticus who have not responded to the usual forms of emergency therapy; seriously ill patients who have previously been thoroughly studied and have frequently been hyposensitized as well, but who have developed severe pollen asthma that resists routine treatment; and a small group of patients with constant, intractable, perennial asthma in whom extensive diagnostic procedures have not led to a specific etiologic diagnosis and in whom all types of routine therapy have produced negligible relief.

METHOD

All patients in this study were hospitalized, first because this procedure is in itself an important therapeutic aid in those severely ill with asthma, and secondly because patients can be studied more quickly and supervised more thoroughly in the hospital; once they are hospitalized, intensive, routine, emergency, antiasthmatic therapy alone often relieves a severe asthmatic attack. All patients were treated in this manner for the first forty-eight hours, and only when they failed to respond was cortisone prescribed. Mention must be made here of the critical case occasionally encountered in which life itself is threatened and in which the time factor is of primary importance. Here cortisone therapy may be started immediately. In the hospital, an etiologic diagnostic program was initiated in each case unless such studies had previously been completed. Carefully taken histories were supported by thorough physical examinations. Inquiry was made concerning a past history of tuberculosis, gastrointestinal bleeding, diabetes, thromboembolic phenomena and neuropsychiatric crises — all of which are possible contraindications to cortisone therapy. The following laboratory data were obtained in all patients: roentgenogram of the chest, urinalysis, complete blood count and fasting blood sugar. In cases in which maintenance cortisone therapy was considered, additional studies were ordered: an electrocardiogram, determinations of vital capacity, circulating eosinophils, blood sodium, potassium, chloride, nonprotein nitrogen and frequently glucose tolerance tests. In the older patients, roentgenograms of the weight-bearing parts of the skeletal structure were taken as a check on osteoporosis. All patients were placed on a diet moderately low in sodium before cortisone was begun, and were weighed daily until discharge.

DOSAGE

No standardized cortisone dosage schedule proved adaptable to all patients. Good-sized initial dosage was necessary for complete clearing of severe asthma in most cases. If patients were not rendered absolutely symptom free at the outset, subsequent maintenance therapy, when attempted, was found unsatisfactory.

OBSERVATIONS

A common and serious situation is that of the patient in status asthmaticus. The physician may make his first acquaintance with such a patient in the home, the office or the hospital, with little to guide him in the way of background. The problem is one of providing rapid symptomatic relief. Such

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The Cortone Acetate used in this study was furnished through the courtesy of Merck and Company, Incorporated, Rahway, New Jersey.

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a patient should be hospitalized at once. If he fails to respond to the usual intensive therapy, cortisone may be considered. In these severe cases we have found the following dosage schedule useful: for the first twenty-four hours, 75 mg. every six hours, orally or intramuscularly; second twenty-four hours, 50 mg. every six hours, orally or intramuscularly; 50 mg. every six hours until the patient shows marked improvement; and finally, 25 mg. every six hours until the asthma clears.

Most cases clear in five to seven days on such a regime. One patient, however, required fourteen days before the asthma entirely subsided. If maintenance cortisone therapy was not to be tried once the asthma had cleared, the dosage was reduced gradually within a few days and then discontinued.

Unfortunately, cortisone was not always successful in every case.

J. S., a 46-year-old married woman, from early childhood to the age of 30 had had annual hay fever and asthma, considered to be on an extrinsic basis and readily controlled by prolonged pollen and dust hyposensitization. Asthma practically disappeared at the age of 30, but returned in moderate degree in 1950 at the age of 45. On August 18, 1951, at the age of 46, while cruising off the shores of Cape Cod in a small boat, she was drenched in a sudden storm so severe that there was considerable fear of running on the rocks. Shortly thereafter, asthma appeared and became steadily worse throughout the following day. By August 20, 36 hours after onset, epinephrine was no longer effective; the boat was put in at the nearest port, and the patient rushed to the hospital by ambulance.

Physical examination showed a well developed, tanned, tense woman with severe dyspnea, "tight" asthmatic breathing, emphysema, a dry tongue, rapid pulse, normal blood pressure and no cyanosis — a picture of severe status asthmaticus. There was no history and no evidence of cardiac involvement. A striking impression was conveyed of an abnormally high degree of apprehension. She stated again and again that her mother had died of asthma and that she would soon do likewise.

Laboratory studies demonstrated circulating eosinophils of 27 per cubic millimeter, chloride of 95 milliequiv., potassium of 4.6 milliequiv. and sodium of 132 milliequiv. per liter. The white-cell count was 14,200, 71 per cent neutrophils, 15 per cent lymphocytes, 9 per cent monocytes, 3 per cent eosinophils and 1 per cent basophils. The urine was normal. The vomitus was guaiac negative. An x-ray film of the chest taken with a portable machine was unsatisfactory because of motion but showed no obvious disease.

The patient was provided with special nurses and was placed immediately on intensive conservative therapy including 5 per cent intravenous infusions of glucose containing 0.5 gm. of aminophylline per liter. Sedation did not relieve the tenseness. On August 21 her condition became worse so she was given 20 mg. of ACTH in 1 liter of 5 per cent glucose at a rate of 30 drops a minute. This was repeated within 12 hours, with no favorable response. On August 22, 100 cc. of adrenocortical extract was administered intravenously in 100 cc. of 5 per cent glucose over a 60-minute period. At 8:15 p.m. 300 mg. of cortisone was prescribed intramuscularly, divided into 4 sites of 75 mg. each. Oxygen by tent was employed intermittently, with no apparent effect upon the patient's color. Breathing gradually became shallower, and the pulse weaker, and she died at 5 a.m. on August 23.

Autopsy showed thick, tenacious plugs of mucus down to the small bronchioles and a moderate degree of cor pulmonale.

Most physicians whose practice includes patients with pollen asthma are familiar with the occasional case in which severe, incapacitating, seasonal asthma develops in spite of hyposensitization therapy and other established forms of treatment. Routine hospital treatment usually brings about gradual relief, and yet the asthma frequently recurs upon discharge unless the pollen season is at its end. Here cortisone can hasten recovery and reduce hospital days, and may also be continued in maintenance doses, thereby keeping the patient asthma free until the end of the pollen season.

M. L., a 40-year-old woman who was separated from her husband, had had her first attack of asthma in July, 1925, at the age of 13. This was mild and cleared within a few weeks. It recurred in June of the following year, when it was accompanied by hay fever, and continued until frost. This pattern persisted for the following 10 years; in August, 1935, the asthma became so severe that hospitalization was necessary. Asthma of varying intensity persisted thereafter from May to frost each year. Scratch tests to grasses and ragweed were markedly positive. Hyposensitization to grasses and ragweed was started in 1947. In that year the patient did well, but in 1948 she was admitted to the hospital once in July and once in August for periods of more than 1 week on each occasion. In 1949 and 1950 hyposensitization to grasses and ragweed was followed by satisfactory relief, but she required hospital admissions of over 1 week in both July and September, 1951, in spite of similar therapy. In May, 1952, hyposensitization to grasses failed to such an extent that hospital care was necessary.

Physical examination showed severe asthma, with a chest full of inspiratory and expiratory wheezes. Because no improvement occurred during the first 3 days, she was placed on cortisone in the following doses: first 24 hours, 75 mg. orally every 6 hours; second 24 hours, 50 mg. orally every 6 hours; third 24 hours, 25 mg. orally every 6 hours.

She was discharged from the hospital after the 3d day, given 25 mg. every 8 hours on the 4th day, and continued with 25 mg. daily thereafter until the grass season was over. Cortisone was then discontinued. In late August, at the height of the ragweed season, the asthma again became severe. This time she needed only 2 days of hospitalization, since the asthma cleared after 500 mg. of cortisone. The dosage was then gradually reduced and she was kept asthma free on 25 mg. daily until the end of the ragweed season, when cortisone was finally discontinued.

There is a distressing group of people with asthma in whom it is often impossible to incriminate any specific antigen or group of antigens. Asthma in these cases often first appears in the fourth decade of life. This group includes a small number of patients whose asthma becomes so persistent and severe that their general health fails and they are incapable of any normal function in society. They frequently require long periods of hospitalization and are never really free from asthma in spite of the customary types of intensive treatment. Fourteen such patients were restored to a useful life by means of cortisone.

M. D., a 56-year-old widow, first had asthma in 1926 at the age of 29 (2 months before the birth of her 3d child). For the duration of her pregnancy, wheezing was mild and easily controlled, but after delivery asthma became more severe and during the following 4 years recurred in monthly attacks. Three of these attacks were severe enough to require hospital admission. For the next 19 years asthma persisted, but she managed to perform her household duties. In December, 1949, at the age of 53, her asthma became constant and intractable. During the next year and a half she was admitted to the hospital eleven times. Many physicians saw her during this period, but no one was able to be of much assistance. When corticotrophin and cortisone first became available, she received several short courses of each, always with marked improvement, but the asthma repeatedly became incapacitating within a few days after withdrawal of the hormones. On May 18, 1951, she was again admitted to the hospital in status asthmaticus, and upon failure to improve on conserv-

ative treatment was considered for maintenance cortisone therapy.

The past history was noncontributory. A sister had urticaria, and a brother had hay fever.

Physical examination showed a poorly nourished woman who looked older than her stated age and who was sitting up in bed gasping for breath and wheezing. The weight was 85 pounds. The anteroposterior diameter of the chest was increased, and motion of the diaphragm was limited. The lungs were hyper-resonant and were filled with inspiratory and expiratory wheezes and rhonchi.

The pulse was 116, and the respirations 30. The blood pressure was 170/90.

The venous pressure was equivalent to 48 mm. of saline solution. The vital capacity was 1.8 liters in 3 seconds. Roentgenographic and fluoroscopic examinations of the chest revealed, bright, full lungs and limited motion of the diaphragm. Roentgenograms of the sacral area showed osteoporosis. The circulating eosinophils were 434 per cubic millimeter. Routine urinalysis, a complete blood count and an electrocardiogram were within normal limits. Multiple scratch and intradermal tests were negative. The blood chemical studies were within normal limits.

The asthma cleared in 5 days on a total intramuscular dose of 0.725 gm. The patient was kept asthma free with daily doses of cortisone to January 27, 1953. An effective daily dose was established by lowering of the arbitrarily given dose every 2 weeks until asthma returned. By this method, the minimal effective dose proved to be 25 mg. of cortisone intramuscularly every 12 hours. Repeated attempts through months of therapy to lower the dose below such a level failed, since the asthma always returned; at no time, however, has this patient required more than 25 mg. of cortisone every 12 hours to remain symptom free.

The mean daily dose for the group of 14 patients is about 50 mg. every 24 hours. In each patient the daily total dose, as well as the dosage interval, has had to be determined by repeated trial and error, for the original severity of symptoms was found to be no guide to optimal daily dosage. If the dose of cortisone was reduced below its minimal effective level, an increase to 200 mg. daily proved advisable until the asthma cleared.

Pharmacologic Effects

Since cortisone is probably used in doses larger than the amount usually found in the normal person we prefer to think of its actions, both good and bad, as pharmacologic rather than physiologic.

Most patients with severe asthma can be rendered symptom free with cortisone. Fourteen patients with severe, persistent asthma in whom no etiologic diagnosis could be established were kept free of asthma for nineteen months. In the one exception the patient usually has some mild wheezing, but he has considerable emphysema of a permanent type. Even he is gainfully employed as a carpenter, whereas he had been idle for many months before therapy.

All the 14 patients on long-term cortisone treatment have gained weight, but only 2 have so far exceeded their previous maximum weights. In all these patients minimal rounding of facial contours has developed. One has grown a small amount of facial hair, and another has some acne; still another has noted an increase in libido. Of the women who have not reached the menopause, little change has been noted in the menstruation. There have been no significant alterations in blood pressure; no abnormal glucose tolerance curves or hyperglycemia has developed. No significant changes in blood sodium, potassium, chloride, carbon dioxide, nonprotein nitrogen or glucose have been found although monthly determinations of each have been made throughout the entire study. The changes in circulating eosinophils have been irregular so that no worthwhile conclusions can be drawn from these figures. Six patients have been studied by a psychiatrist without any evidence of basic mental changes. None of the 14 have shown any psychiatric disturbances other than mild euphoria.

Roentgenograms of the lumbosacral areas of most of the older patients before cortisone therapy disclosed osteoporosis, but recent films have failed to demonstrate any increase in this process. Exercise tolerance and three-second tests of vital capacity have increased in all patients.

Complications

Some problems that arose were probably not due to the cortisone. All patients have had respiratory-tract infections, and in December, 1951, 1 patient had a tracheobronchitis that required hospitalization. In 2 other cases abscesses at the sites of cortisone injection developed. In October, 1951, a cheilosis, which cleared on vitamin therapy, occurred in 1 of these.

Discussion

The use of cortisone in severe asthma involves the treatment of a disease as yet imperfectly understood with a potent hormone whose mode of action remains a mystery. Emphasis must therefore be placed upon the advisability of employing this agent only in selected cases and upon the necessity for careful supervision throughout treatment.

Decision to employ maintenance cortisone therapy in patients chronically ill with persistent, perennial asthma presumably implies committing these people to long periods of such treatment. It is our belief that these patients should be checked routinely. This involves at least a bimonthly physical examination, instructions to report deviations from the normal pattern whenever they occur and periodic blood chemical tests. Such patients should remain on a diet moderately low in sodium in which the caloric value is adjusted to particular needs. Experience with this small but carefully controlled group indicates that it is possible to maintain patients with severe chronic asthma on cortisone for periods up to nineteen months without any serious difficulty and with striking symptomatic relief. It is appreciated that the number of cases in this study is small and that complications may arise at a later date.

Used with discretion, cortisone has proved one of the most useful agents available for the therapy of severe asthma. When the mode of action of this

agent is finally understood, more may be learned about the pathologic process that it so successfully controls.

Summary and Conclusions

Cortisone has been found useful in the therapy of 14 selected cases of severe bronchial asthma. Selection of cases is discussed.

The hormone may fail to relieve severe asthma and even to save life in certain cases.

The problem of dosage varies with each patient. In general, enough of the hormone must be prescribed initially until it relieves all symptoms of asthma; daily dosage is then reduced to a minimal level that will maintain freedom from wheezing.

In the severe, perennial type of asthma in which no definite etiologic diagnosis can be made and in which the usual forms of therapy have failed, maintenance cortisone therapy over a period of many months has proved useful. In these cases, certain problems of dosage have arisen: if, on a lowered dosage, asthma returns or becomes more severe, larger doses are indicated (it has often been found advisable to return to initial high doses and then to reduce the amount gradually to a suitable-maintenance dose); no patient has been kept asthma free on less than one 25-mg. daily dose of cortisone; once the optimal daily dose has been established, its level does not seem to fluctuate materially either up or down; complications and undesirable effects have been minimal during a period of many months of cortisone therapy — strict supervision is essential for success.

References

1. Carryer, H. M., et al. Effect of cortisone on bronchial asthma and hay fever occurring in subjects sensitive to ragweed pollen. *J. Allergy* **21**:282-287, 1950.
2. Randolph, T. G., and Rollins, J. P. Effect of cortisone on bronchial asthma. *J. Allergy* **21**:288-295, 1950.
3. Carey, R. A., Harvey, A. M., Howard, J. E., and Winkenwerder, W. L. Effect of adrenocorticotropic hormone (ACTH) and cortisone on course of chronic bronchial asthma. *Bull. John Hopkins Hosp.* **87**:387-414, 1950.
4. Segal, M. S., and Herschfus, J. A. Progress in allergy: ACTH and cortisone in management of hypersensitivities, with particular reference to bronchial asthma: review of clinical and laboratory studies. *Ann. Allergy* **8**:786-798, 1950.
5. Thorn, G. W., et al. Clinical usefulness of ACTH and cortisone. *New Eng. J. Med.* **242**:783-793, 1950.
6. Schwartz, E. Oral cortisone in intractable bronchial asthma. *J. A. M. A.* **147**:1734-1737, 1951.
7. Cooke, R. A., et al. ACTH and cortisone in allergic diseases: clinical serologic (electrophoretic) and immunologic studies. *J. Allergy* **22**:211-236, 1951.
8. Baldwin, H. S., and deGara, P. F. Hospital and ambulatory treatment of asthma and eczema with ACTH and cortisone. *J. Allergy* **23**:15-26, 1952.
9. Franklin, W., Lowell, F. C., Schiller, I. W., and Beale, H. D. Clinical studies with cortisone by mouth, cortisone by injection, and ACTH in treatment of asthma. *J. Allergy* **23**:27-31, 1952.
10. Burrage, W. S., Irwin, J. W., and Gibson, J. S. Maintenance cortisone in severe bronchial asthma. *J. Allergy* **23**:310-321, 1952.

MEDICAL PROGRESS

UROLOGY

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IN recent years a better understanding of certain conditions that affect the genitourinary organs has developed. Advances in the control and elimination of infections have been spectacular, and the necessity of adequate treatment in the acute stage of infections that involve the kidney, by means of which the irreversible changes of chronic pyelonephritis may be prevented, has been emphasized. Better methods have been devised to aid in the differentiation of benign renal lesions and neoplastic disease through roentgenographic visualization of the blood supply of the kidney. Urology has shared the general trend in surgery, paced by the gynecologists, and has tended to become more radical in the surgical treatment of malignant neoplasms. With the increased number of injuries of the genitourinary organs resulting from military activity more experience has been gained in their proper management. The treatment of genitourinary tuberculosis is now considerably more effective than in the past, owing to an appreciation of the necessity for general care of the tuberculous patient together with the development of new antituberculosis drugs.

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Infections of the Urinary Tract

The results of treatment of infections of the urinary tract with the various antibiotics have been outstanding, but it has been pointed out that these agents are not an unmixed blessing.[1] These newer antibacterial substances have not lessened the importance of a definite diagnosis although such an attitude has often been the tendency. Other drawbacks have been the emergence of bacteria that are resistant not only to one antibiotic but simultaneously to several. This has been particularly true of the staphylococci.[2] Superinfections by other bacteria have occurred during antibiotic therapy sometimes by organisms not ordinarily pathogenic but at times difficult to eradicate, such as monilia. Despite the quick response of many urinary-tract infections, some either do not respond or recur. The reasons for this are several. Many of the failures are due to the presence of obstructive lesions. Congenital abnormalities, calculous disease, divertic-

ula, strictures and prostatism are the commonest. Associated lesions of the large bowel or pelvic organs account for others, and tuberculosis for a few. Infections that fail to clear after adequate initial treatment or recur after treatment require careful investigation. In addition, certain bacteria are resistant to modern therapy. These are chiefly *Bacillus pyocyaneus* (*Pseudomonas aeruginosa*) and many strains of *B. proteus* (*Proteus vulgaris*).

Treatment

The first step in the treatment of urinary-tract infections is identification of the organisms. Initial therapy may be guided by a stained smear of the urinary sediment. If streptococci or staphylococci are present penicillin or procaine penicillin G in sesame oil, 300,000 units intramuscularly a day for five days, is indicated. Many staphylococci (about 68 per cent) are now said to be resistant to penicillin, and some other agent must be used.[3] The majority of acute urinary infections are caused by gram-negative bacilli, *Escherichia coli* being the offender in 60 to 80 per cent. Since this is true, the initial treatment usually should be one of the sulfonamides such as sulfadiazine or Gantrisin. The latter has great solubility and little toxicity when given in doses of 1 or 2 gm. every six hours for seven to ten days. Such simple treatment is continued until the invading organisms are identified by culture and their sensitivity to the various antibiotics has been determined. Therapy is then continued as indicated. It has been pointed out that treatment should be carried out vigorously from the standpoint of both dose and duration.[4]

Authorities have differed somewhat regarding the effectiveness of the various therapeutic agents but according to recent literature some of their characteristics are as follows:

The sulfonamides. These drugs maintain a useful place in the treatment of urinary infections in spite of the development of the newer antibiotics. The more recent preparations of sulfonamides, with their greatly increased solubility, have shown little or no tendency toward crystalline precipitation, and toxic reactions have been few. Some patients, however, are sensitive to any of the sulfonamides. Gantrisin (3, 4-dimethyl-5-sulfanilamido-isoxazole) is commonly used. It is effective in most uncomplicated infections due to *Esch. coli* and against some strains of *P. vulgaris*. Infections due to *Streptococcus faecalis*, *Ps. aeruginosa* and *Aerobacter aerogenes* are not benefited. The usual dose of Gantrisin is 2 gm. by mouth every six hours for five to ten days. It may be given intramuscularly or intravenously in 40 per cent solution. Fluids need not be forced, and alkalies are not necessary.

Penicillin. This antibiotic is effective against gram-positive organisms such as staphylococci and streptococci. It is not effective in *Str. faecalis* infections, however. The increasing incidence of penicillin-resistant staphylococci must be remembered. Penicillin is usually given as procaine penicillin G, 300,000 units intramuscularly a day for about five days. Oral preparations are also said to be highly effective in doses of 100,000 to 400,000 units two or three times a day. Hypersensitivity to penicillin occurs in 1 or 2 per cent of patients.

Streptomycin. This antibiotic is effective against infections caused by gram-negative organisms especially *Esch. coli*, *A. aerogenes* and the Friedländer bacillus (*Klebsiella pneumoniae*). Some strains of *P. vulgaris* and *Ps. aeruginosa* have responded. Streptomycin has certain disadvantages. For urinary infections it must be given intramuscularly. It is toxic to the vestibular branch of the eighth cranial nerve, and dihydrostreptomycin affects the auditory branch. Sensitive organisms quickly become resistant to streptomycin. It is recommended that 1 gm. be given daily as a single dose. Streptomycin is many times more effective if the urine is kept alkaline by 4 cc. of a 50 per cent sodium citrate solution or 4 gm. of sodium bicarbonate, three or four times daily.

Aureomycin. Infections caused by *Esch. coli*, *Staphylococcus aureus* and *Str. faecalis* respond well to aureomycin. It is especially useful against penicillin-resistant staphylococci. Most writers have found aureomycin ineffective against infections due to *P. vulgaris* and *Ps. aeruginosa*. Like streptomycin, it is very effective against the Friedländer bacillus. The most common unfavorable reactions to aureomycin, terramycin and chloramphenicol are those of the gastrointestinal tract, their incidence being in the order given. These reactions are lessened if food or milk is taken with each dose. Aureomycin may be given intravenously but daily doses of 2 gm. may cause liver damage. It is advised that components of the vitamin B complex be given with aureomycin, terramycin and chloramphenicol to lessen the incidence of stomatitis and proctitis. The recommended dose of aureomycin for urinary-tract infections is 500 mg. every six hours for seven days.

Terramycin. Infections due to *Esch. coli*, *Str. faecalis* and *A. aerogenes* respond well to terramycin. Some strains of *Ps. aeruginosa* are said to have responded favorably, but the drug is ineffective in infections due to *P. vulgaris*. The dose and unfavorable reactions are similar to those of aureomycin.

Chloramphenicol. At the present time, this antibiotic is under scrutiny because of reported cases of injury to the hematopoietic system. Since it has been effective against both gram-positive and gram-negative organisms judgment whether chloramphenicol may be used or not should perhaps be reserved until the doses employed and the duration of treatment have been stated when serious reactions have taken place. The drug has been effective against infections caused by *Esch. coli* and *Str. faecalis*. It has been reported as effective against some strains of *Ps. aeruginosa* and *A. aerogenes* but it has

not been effective against *P. vulgaris*. The dose and untoward reactions are similar to those of aureomycin.

Neomycin and polymyxin. Although these antibiotics are said to be effective against infections due to certain organisms that are resistant to other agents, such as *Ps. aeruginosa*, their usefulness is restricted because of their toxicity. However, they may be used in reasonable doses, if necessary. Polymyxin may be given intramuscularly in doses of 2.5 mg. per kilogram of body weight daily for seven days. Neomycin may be given by mouth, 250 mg. every six hours for seven days.

Erythromycin. This recently discovered antibiotic is reported to be effective against streptococcal infections and penicillin-resistant staphylococcal infections. It is not effective against those due to *Esch. coli*, *P. vulgaris* or *Ps. aeruginosa*. The dose of erythromycin has been given as 200 to 500 mg. initially followed by 100 to 250 mg. every three or four hours.

Mandelamine (*methenamine mandelate*). A combination of mandelic acid and methenamine, this drug has been useful in *Esch. coli* and certain streptococcal urinary-tract infections. No reactions have been reported from its use. The dose is 3 tablets four times daily. Fluids need not be forced, and no other acidifying agents are necessary.

In summary, the important features in the treatment and control of infections of the urinary tract are the recognition and elimination of complications such as urinary stasis, stones, neoplasms and tuberculosis; identification of the causative organisms and their sensitivity to the various antibacterial agents; and adequate initial and sufficiently prolonged administration of the indicated agent. Chronic infections that have not yielded to one antibiotic may respond to combined therapy.[1-9]

Diseases of the Kidney

Acute and Chronic Pyelonephritis

Recent evidence has confirmed the fact that the kidney may become infected by a hematogenous spread of bacteria or by an ascending route. Ascending infections occur in pregnancy, spinal-cord injuries with paralysis of the bladder and conditions that produce urinary stasis. The initial lesions of ascending infections are in the collecting portions of the kidney. Hematogenous infections are associated with bacteremia, and the initial renal lesions are in the cortex and medulla. Regardless of the route of infection, however, lesions quickly become widespread throughout the kidney.

In acute pyelonephritis multiple inflammatory foci are scattered throughout the interstitial tissue. These begin as collections of polymorphonuclear leukocytes and monocytes adjacent to blood vessels. They may progress to abscess formation. In the acute stages the glomeruli are uninvolved, but the tubular system may be invaded. An extreme example of acute infection is necrotizing renal papillitis in diabetic patients. Chills, fever, costovertebral-angle tenderness and dysuria suggest acute pyelonephritis, and pyuria or bacilluria confirms the diagnosis. However, the urine may be clear while the temperature is rising, and pyuria and bacilluria may be intermittent. As long as the interstitial tissue alone is affected the urine will remain clear. In the absence of urinary stasis pyelonephritis usually runs a short course. The condition responds quickly to specific therapy, and the lesions heal. Recurrent episodes of acute pyelonephritis suggest repeated new infections or incomplete healing. Each attack results in increased damage to renal tissue, ending eventually with the dire results of chronic pyelonephritis. To avoid this the treatment of acute pyelonephritis should be aggressive enough not only to sterilize the urine but also to eradicate the infection in the interstitial tissue of the kidney.

Chronic pyelonephritis is the result of repeated attacks of acute pyelonephritis or of long-standing smoldering infection. The kidneys are shrunken and scarred and difficult to distinguish from the congenital hypoplastic kidney.[10] The renal tubules are dilated, lined with flattened epithelium and filled with colloid-like casts. Arterial changes are prominent, and many of the glomeruli are hyalinized and fibrosed. Such changes are irreversible. Since there is often little or no evidence of active infection in chronic pyelonephritis its diagnosis may be difficult. Laboratory methods help, however, by showing some impairment of renal function, a urine of large volume and low specific gravity, and albuminuria. The urinary sediment often contains many leukocytes, but cellular elements may be few. Repeated cultures usually give evidence of infection. The specific treatment of chronic pyelonephritis consists of determining whether active infection is still present. If bacteria are found by smear or culture appropriate antibiotics are given and continued until the urine is sterile. Usually, it is advisable to continue treatment with small amounts of one of the antibiotics for weeks or months. Although the usual course of chronic pyelonephritis is one of slow progression, some patients undoubtedly recover, for spontaneous cure has been reported in about 20 per cent.[11] *The best way to avoid chronic pyelonephritis is treatment when the infection is in the acute stage.*[12]

Neoplasms of the Kidney

Most new growths of the kidney are malignant. Those that are benign, such as adenomas, fibromas and hamartomas, are unusual and can seldom be diagnosed before operation. The commonest malignant tumor of the renal parenchyma is the renal-cell carcinoma or hypernephroma. These neoplasms often produce no symptoms until they have reached a considerable size or have already spread to other

parts of the body. Dissemination is by the blood stream, chiefly to the lungs and bones, or by the lymphatics to regional lymph nodes.

Because of the lack of symptoms an early diagnosis of renal-cell carcinoma has been difficult. The more frequent use of intravenous urography, however, has demonstrated an increasing number of renal abnormalities that are suspicious of neoplasm. But it has often been impossible by intravenous or retrograde pyelography to know whether one was dealing with a benign or a malignant lesion. The differentiation of simple cyst and neoplasm has been especially difficult. Considerable help in this problem has been given through roentgenographic visualization of the renal blood supply by lumbar aortography. Although puncture of the abdominal aorta and injection of a contrast solution sounds formidable, this procedure has been carried often enough to prove that, when intelligently used, it is relatively simple and safe. In my experience, 30 cc. of 70 per cent Urokon solution rapidly injected into the abdominal aorta has satisfactorily indicated the arterial blood supply of the kidneys and in addition has provided nephrograms that bring out the renal outlines. As familiarity with this method increases there is every reason to believe that it will aid in the differentiation of benign and malignant kidney lesions and detect various obscure abnormalities of the renal blood supply.[13, 14]

Together with the advances made in the diagnosis of renal neoplasms better methods are available for their treatment. For many years the lumbar approach was used to remove tumors of the kidney. Transperitoneal nephrectomy was then employed and is still favored by many. Important features for the successful removal of large renal neoplasms are adequate exposure, control of hemorrhage, access to the blood supply of the kidney without disturbing the tumor mass and complete removal of the perirenal tissues and regional lymph nodes. These requirements, it is believed, are best met by the thoracoabdominal approach. During the past four years many patients have been operated upon through this incision, with a low mortality and morbidity. There is an increasing tendency to favor the thoracoabdominal approach for the removal of renal neoplasms.[15]

Diseases of the Ureter

Megaloureter

Congenital dilatation of one or both ureters is not too uncommon in infancy and childhood. Two different varieties are described by Campbell[16]: congenital hydroureter in which the terminal portion of the ureter is narrowed and there is no reflex up the ureter, and dilatation in which the ureteral orifices are gaping and reflex occurs.

The etiology of megaloureter has been obscure, and its treatment has been generally unsatisfactory. Some have thought that either arrested muscular development or neurogenic dysfunction might be the cause, but these theories have lacked proof. A new and interesting concept of etiology, arising from the association of megalobladder and megaloureter with megacolon, has been proposed by Swenson et al.[17]

Since Hirschsprung's disease has been shown to be due to absent peristalsis in the rectosigmoid because of an absence of the ganglion cells of Auerbach's plexus in this segment of the bowel, it was thought that some of these patients might have a similar defect in the innervation of the bladder muscle. It seemed reasonable that there might be some patients in whom this defect existed in the bladder only and that these were the patients with megaloureters.

Histologic studies were made of 7 bladders from infants and children who had shown the characteristic features of megalobladder and megaloureter clinically and at autopsy. An attempt was made to estimate the number, character and distribution of ganglion cells in all parts of these bladders as compared with normal bladders. A diminution in the number and size of the ganglions and in the number and variety of nerve cells and number of nerve bundles was observed in 6 of the 7 abnormal bladders. It was clearly stated that ganglion cells are limited normally to certain areas of the bladder and that they may be missed in block sections. Studies of ganglion cells in the ureters were unsatisfactory since normal ureters contain only occasional ganglion cells.

These investigators believed that the diminution of parasympathetic ganglion cells in the bladder might be the fundamental lesion in megalobladder associated with Hirschsprung's disease and that in some patients with megaloureters this might be the cause of bladder dysfunction. Megaloureters resulted from the poor bladder function in a similar way that the ureters become dilated in long-standing cord bladders.

No ideal method of correcting this deformity has been found. Prolonged drainage of the bladder for four to eight months, however, resulted in general improvement of these patients, a diminution in the size of the megaloureters and better bladder function. How permanent these benefits may be is not known. Although the work of these investigators has not been substantiated by others their efforts to solve an important and difficult problem are praiseworthy.[17]

Diseases of the Bladder

Tumors of the bladder are not common but they constitute one of the most important lesions of the genitourinary organs. They account for about 0.5 per cent of hospital admissions and for approximately 5 per cent of admissions to the urologic service. Most tumors of the bladder are epithelial, and many retain the characteristics of the normal

transitional epithelium. Although these neoplasms vary in malignancy, many regard them all as cancer.

Carcinoma

In their early stages most tumors involve only the surface layers of the bladder. They do not metastasize since there are no lymphatics in the mucosa, and blood-borne metastases are not common. Such tumors are satisfactorily treated by local destruction. When the bladder muscle is invaded, however, the situation is different. Probably at least 50 per cent of these invasive tumors have already spread to regional lymph nodes. They are difficult to cure.[18]

On the whole, the treatment of these deep-seated tumors of the bladder has been unsatisfactory. Simple cystectomy cured many of the multiple superficial tumors of low malignancy, but few of the invasive tumors were cured because of regional-lymph-node involvement. The addition of dissection of the pelvic lymph nodes to total cystectomy has been a reasonable step in line with recent advances in the treatment of malignant lesions. Although it is still too early to evaluate this radical program many have wondered whether it would significantly improve the long-term cure rate. One of the chief problems has been the best method of diverting the urine.

The most reasonable way of disposing of the urine seemed to be transplantation of the ureters to the large bowel. At first, ureterosigmoidostomy carried a high mortality, but as surgical technic improved and antibiotics were developed the operation became feasible. In spite of good functional results, however, it was soon recognized that severe changes in the electrolyte pattern of the blood resulted from this procedure. Usually within the first six months, many of these patients manifested anorexia, weakness, nausea and vomiting, weight loss and other symptoms of azotemia. Studies showed that this was caused by hyperchloremic acidosis. Low serum potassium levels were accompanied by characteristic electrocardiographic changes. Nitrogen retention was present. These serious chemical imbalances were obviously due to the absorption of waste products by the large bowel and perhaps also to impaired renal function from repeated attacks of pyelonephritis. Although patients might be cured of cancer many died within a five-year period in uremia from chronic pyelonephritis and failing renal function. The same changes have been reported after the surgical correction of exstrophy.[19-21]

These adverse circumstances have lessened the enthusiasm for total cystectomy. Nevertheless, there are times when this operation alone offers the patient any chance of cure, and then it is entirely justifiable. Efforts to utilize isolated segments of bowel to serve as a reservoir for urine have not been too successful. Present tendency in many clinics is to favor cutaneous ureterostomy over ureterosigmoidostomy. Considerable more work must be done before this difficult problem is solved.

Diseases of the Prostate

The prostate is the most important of the male accessory sex glands. Essentially a glandular structure, it is subject to certain diseases chiefly inflammation, benign hypertrophy and carcinoma. The tendency for tumor formation to take place in the prostates of men over fifty years of age makes this organ one of outstanding interest. First in importance is carcinoma.

Carcinoma

Figures from many sources indicate that the incidence of cancer of the prostate is surprisingly high. Of every 100 men who reach the age of sixty it has been said that 5 will develop cancer of the prostate. Pathological studies have confirmed the high incidence of prostatic cancer. In 292 consecutive autopsies on men fifty years or more of age Rich[22] found frank carcinoma in routine sections in 14 per cent. Moore[23] reported an incidence of 20.5 per cent in men over fifty with an increasing incidence in the later years of life to 29 per cent. Examination of the entire gland of 50 consecutive men over fifty years old by Baron and Angrist[24] showed cancer in 46 per cent. The foci of carcinoma found in these glands were often small, and their actual significance is not clear. For years, however, it has been true that cancer is present in about 20 per cent of patients who have symptoms of prostatic obstruction.

Treatment of the malignant prostate became considerably modified in 1941 by the work of Charles Huggins,[25] who demonstrated the beneficial effects of androgen control on patients with prostatic cancer. Reduction of androgen activity either by castration or through the administration of estrogens resulted in marked clinical improvement in most patients. Years were added to their lives, and symptoms were relieved even in the presence of extensive metastatic disease. Unfortunately, however, these measures proved to be temporary and not curative. After varying lengths of time, months or years, the cancer cells again became activated, and symptoms returned. Total prostatectomy at an early stage of tumor development remained the only method that offered any chance of cure.

Bilateral adrenalectomy. It was thought that the adrenal glands might play a role in increased androgen activity and the reactivation of prostatic cancer. It was known that steroid hormones were formed to a considerable extent in the adrenal glands. More than 28 steroid compounds have been isolated from the adrenal cortex. They are in three functional groups: the desoxycorticoids, which affect electrolyte exchange; the 11-oxysteroids or glucocorticoids, which have a profound effect upon protein and carbohydrate metabolism; and the andro-

sterones, which have an anabolic effect on protein metabolism. The aim of bilateral adrenalectomy is the elimination of effective androgens.

The first successful total bilateral adrenalectomy in man for metastatic cancer of the prostate was reported by Huggins in 1945. Although the patient was improved, adrenal insufficiency developed, for cortisone was not available. With effective substitution therapy provided by cortisone and desoxycorticosterone bilateral adrenalectomy has been performed successfully in many cases.

At present the best response to bilateral adrenalectomy for cancer of the prostate seems to have been obtained in patients who have had a remission after castration and estrogen therapy and when the primary tumor in the prostate has regressed. Often symptomatic relief is immediate. Severe pain disappears, and some totally incapacitated patients again become active. This is said to have occurred in about 50 per cent of patients. There is no evidence that this procedure is curative, and in many cases the beneficial effects of bilateral adrenalectomy have been temporary. It is too early to evaluate this operation, but considerable thought should be taken before a patient is subjected to a procedure that entails the risk of Addison's disease and necessitates permanent replacement therapy.[25-27]

Diseases of the Testis

Interest in lesions of the testis centers on neoplastic disease, for this includes one of the most dangerous lesions of the male: malignant tumor. Benign new growths are uncommon and significant only because they can seldom be differentiated preoperatively from malignant growths. Malignant tumors have been classified and reclassified, but confusion has been lessened by a recent simple classification by Moore[28] according to four basic cellular types: adult teratoma, seminoma, embryonal carcinoma and choriocarcinoma (chorioepithelioma). Each cellular type may occur singly or in combination with any or all of the other three.[28]

Treatment of these tumors depends upon the cellular components. Adult teratomas are slow-growing neoplasms and constitute less than 10 per cent of testicular neoplasms. Although they occasionally contain malignant elements, adult teratomas usually are adequately treated by orchidectomy. Seminomas are one of the most common tumors, accounting for about 30 per cent. They occur at a later age than the other neoplasms and have some tendency to be bilateral. Seminomas are so radiosensitive that most authorities treat them by orchidectomy followed by external irradiation, with good results. Embryonal carcinomas are highly malignant neoplasms that often metastasize to regional lymph nodes early in their development. Simple orchidectomy has cured only a small percentage of embryonal carcinomas, and many are radioresistant. There has been renewed interest in radical surgery in the treatment of these malignant tumors. This consists of removal of the primary tumor and dissection of the regional lymph nodes. Since the lymphatic drainage from the testis is to lymph nodes along the vena cava and aorta to the region of the renal blood vessels this operation is best accomplished through a thoracoabdominal incision.[29-32] Choriocarcinomas are rapidly growing tumors with a poor prognosis. They are characterized by early wide dissemination, lack of radiosensitivity and high titer of gonadotropin in the urine. Fortunately, pure choriocarcinomas comprise less than 1 per cent of testicular neoplasms since they are usually fatal within a short time.

Injuries of the Genitourinary Organs

Recent years have seen a lower mortality and better end results in injuries of the genitourinary organs. Increased experience gained from the various theaters of war and improved surgical technic, with adequate blood replacement and control of infection, have been responsible.

Kidney

Most injuries to the kidney are from falls, body-contact sports, crushing injuries, direct blows on the flank, automobile and coasting accidents and gunshot wounds. These injuries may be mild or serious. Treatment depends upon the extent of damage to the kidney. An accurate diagnosis in this respect, therefore, is important. Intravenous pyelography may provide all the necessary information, but if this is not adequate retrograde pyelography should be performed when circumstances permit. Conservative treatment in general has been adopted in the treatment of renal injuries. There are, however, definite indications for operation. If the patient's condition is deteriorating, with a falling blood pressure, evidence of increasing hemorrhage, a growing mass in the flank and a retrograde pyelogram that shows considerable extravasation of the dye, operation should be performed. When large blood vessels are ruptured immediate nephrectomy is indicated if the condition of the patient permits. Shock must be treated first. In war wounds renal injuries are usually accompanied by damage to intraperitoneal structures, and attention to these organs comes first.[33-35]

Ureter

Because it is well protected by the muscular and skeletal structure of the body the ureter is seldom injured by external violence. Damage from war injuries is also rare since the ureter is small and not fixed. Surgical trauma accounts for most ureteral injuries.

Minor damage to the ureter, such as small incisions, often requires no repair, but adequate drainage must be provided since a urinary fistula is to be expected. Extensive damage to one or both

ureters is serious. If the ureter has been ligated, early removal of the suture material may be done on patients who are in good general condition. This may be a formidable procedure in patients recently operated on and generally is not favored. Immediate nephrostomy with subsequent repair is advised. If the ureter is transected, immediate repair should be carried out by end-to-end anastomosis over a splinting catheter. Injuries to the lower ureter may be impossible to repair; reimplantation into the bladder can be done or a tube flap from the bladder may be constructed if the ureter is too short for reimplantation. Ligation of the damaged ureter is not recommended.

All cases of ureteral damage require future care since stricture formation is always possible. The results of ureteral anastomosis in the past include many failures, but good surgical technic and the control of infection should save many kidneys.[36]

Bladder

The bladder may be ruptured by direct blows on the abdomen or penetrating wounds or as a complication of transurethral surgery. Most injuries, however, are associated with fractures of the bony pelvis. In civilian life about 95 per cent of bladder injuries are from this cause, and the bladder or urethra is injured in about 15 per cent of the cases of fractures of the pelvis. The tear is extraperitoneal in 60 per cent and intraperitoneal in 40 per cent.

The diagnosis of ruptured bladder is best made by cystography. About 200 cc. of one of the mediums used for intravenous urography diluted ten times with sterile water is injected into the bladder through a catheter, and anteroposterior and oblique films are taken. Diffusion of the dye outside the bladder makes the diagnosis obvious.

Conservative treatment has no place in rupture of the bladder. Immediate operation is necessary, with evacuation of intraperitoneal fluid, repair of lacerations, control of hemorrhage and suprapubic drainage of the bladder and pelvic spaces.[33, 37]

Male Urethra

Almost all injuries to the male urethra are associated with fractures of the pelvis or are due to straddle injuries. Minor injuries often heal spontaneously aided only by a splinting catheter. Severe injuries are serious surgical emergencies. Urinary extravasation soon takes place, and it is not possible to pass a catheter to the bladder. If extravasation is present an immediate cystotomy must be performed. Areas of extravasation and hemorrhage are adequately drained, and the damaged urethra is repaired as well as possible. The use of male and female interlocking sounds facilitates the establishment of urethral continuity. In addition to cystotomy drainage the bladder is drained by a Foley catheter through the urethra. If the urethra has been severed at the apex of the prostate the catheter is put on traction to eliminate the space between the prostate and the torn membranous urethra. Late injuries to the urethra require careful reconstruction by plastic surgery.[33, 37]

Genitourinary Tuberculosis

Invasion of the genitourinary tract by the tubercle bacillus is only one phase of a disease that tends to spread to many parts of the body, resulting in serious illness, prolonged disability and an uncertain outcome. The initial lesion of genitourinary tuberculosis is probably always in the kidney, but the kidney is always infected by a hematogenous spread of bacilli from some other focus within the body, most frequently the lungs. Intelligent treatment of genitourinary tuberculosis is based on the fact that the renal or genital lesions are but one of many possible manifestations of a systemic disease. Sanatorium care or its equivalent is regarded as necessary for adequate treatment.

The advent of streptomycin modified considerably the treatment of pulmonary and other forms of tuberculosis but to a less extent the genitourinary complications of this disease. It soon became evident that tubercle bacilli quickly become resistant to this drug. Combinations of drugs were then tried, but some, such as amithiozone, proved to have a high degree of toxicity. Para-aminosalicylic acid, although only weakly effective against tuberculosis when used alone, was found to prevent or delay the emergence of resistant bacilli when combined with streptomycin. Terramycin is also said to be useful in this respect. More recently, the hydrazine derivatives of isonicotinic acid have been reported to be effective.

A study of the effect of streptomycin therapy on renal tuberculosis of varying degrees was conducted in England in 1950 by Jacob and Borthwick.[40] Both these investigators are well known for their work in tuberculosis. The conclusions they came to are in agreement, for the most part, with those of others in the management of this disease. The first group of patients studied had clinically unilateral renal tuberculosis without cystitis, and although the renal lesion was considered to be small it was demonstrable by pyelography. In most of these patients (6 of 7) the urine became tubercle negative during treatment. However, the urine was again tubercle positive in 1 a month and in 2 others three and six months after treatment. Positive urines developed in 3 patients in the supposedly healthy kidney during or after treatment. The pyelographic appearance of the lesion improved in 1 patient, became worse in 1 and remained unchanged in the remainder. These observations are in accord with the generally accepted point of view that nephrectomy is indicated in the presence of clinically unilateral renal tuberculosis with a deformity detectable by pyelography. Genital lesions have responded less well to streptomycin therapy.[41]

The sanatorium care of patients with genitourinary tuberculosis now includes 1 gm. of streptomycin intramuscularly twice weekly, 12 gm. of para-aminosalicylic acid (PAS) by mouth daily in divided doses, and one of the derivatives of isonicotinic acid in amounts of 2 to 4 mg. per kilogram of body weight or an average of 100 mg. three times daily for most adults. This routine is followed during the preoperative and postoperative periods of sanatorium care. During the immediate postoperative period daily doses of 1 gm. of streptomycin are administered. Continuous and prolonged treatment is preferred to shorter or repeated courses. The proper duration of treatment has not been determined.

In summary, the essential features of the treatment of renal tuberculosis are sanatorium care supplemented by what have been shown at the present time to be the most effective antituberculous drugs. These are streptomycin, PAS and the hydrazine derivatives of isonicotinic acid. None of the chemotherapeutic agents alone, however, can be depended upon to cure or control an established renal focus of tuberculosis.[42]

References

1. Romansky, M. J., and Kelser, G. A. Antibiotic and chemotherapeutic agents in infections of respiratory tract. *J. A. M. A.* **150**:1447-1449, 1952.
2. Gocke, T. M., and Finland, M. Cross-resistance to antibiotics: effect of repeated exposure of bacteria to aureomycin, terramycin, chloramphenicol or neomycin on resistance to all of these antibiotics and to streptomycin and penicillin. *J. Lab. & Clin. Med.* **38**:719-735, 1951.
3. Nichols, D. R., and Needham, G. M. Aureomycin in treatment of penicillin-resistant staphylococcic bacteremia. *Proc. Staff Meet., Mayo Clin.* **24**:309-316, 1949.
4. Nesbit, R. M., and Baum, W. C. Antibiotic and chemotherapeutic agents in infections of genitourinary tract. *J. A. M. A.* **150**:1459-1462, 1952.
5. Carroll, G., Allen, H. N., and Flynn, H. Gantrisin in treatment of urinary infections. *J. A. M. A.* **142**:85, 1950.
6. Keefer, C. S. Evaluation of antibiotic therapy. *Postgrad. Med.* **9**: 101-105, 1951.
7. Rutenburg, A., and Schweinburg, F. B. Oral administration of aureomycin in treatment of urinary infections. *New Eng. J. Med.* **241**:698-700, 1949.
8. Pulaski, E. J., and Reiss, E. Terramycin and aureomycin in surgical infections: report of two hundred cases. *J. A. M. A.* **149**:35-40, 1952.
9. Haight, T. H., and Finland, M. Laboratory and clinical studies on erythromycin. *New Eng. J. Med.* **247**:227-232, 1952.
10. Emmett, J. L., Alvarez-Ierena, J. J., and McDonald, J. R. Atrophic pyelonephritis versus congenital renal hypoplasia. *J. A. M. A.* **148**:1470-1477, 1952.
11. Braasch, W. F. Clinical data concerning chronic pyelonephritis. *J. Urol.* **39**:1-33, 1938.
12. Birchall, R., and Alexander, J. E. Medical aspects of pyelonephritis. *Medicine* **29**:1-28, 1950.
13. Nelson, O. A., and Mousel, L. H. Renal tumors. *J. A. M. A.* **148**: 171-174, 1952.
14. Smith, P. G., and Evans, A. T. Technique of translumbar arteriography. *J. A. M. A.* **148**:255-258, 1952.
15. Chute, R., Soutter, L., and Kerr, W. S., Jr. Value of thoracoabdominal incision in removal of kidney tumors. *New Eng. J. Med.* **241**: 952-960, 1949.
16. Campbell, M. Primary megalo-ureter. *J. Urol.* **68**:584-590, 1952.
17. Swenson, O., MacMahon, H. E., Jaques, W. E., and Campbell, J. S. New concept of etiology of megaloureters. *New Eng. J. Med.* **246**: 41-46, 1952.
18. Jewett, H. J. Infiltrating carcinoma of bladder: relation of early diagnosis to five-year survival rate after complete extirpation. *J. A. M. A.* **148**:187-189, 1952.
19. Odel, H. M., Ferris, D. O., and Priestley, J. T. Further observations on electrolyte pattern of blood after bilateral ureterosigmoidostomy. *J. Urol.* **65**:1013-1020, 1951.
20. Rosenberg, M. L., and Elliot, J. S. Reabsorptive acidosis following ureterosigmoidostomy. *Stanford M. Bull.* **9**:13-17, 1951.
21. Harvard, B. M., and Thompson, G. J. Congenital exstrophy of urinary bladder: late results of treatment by Coffey-Mayo method of uretero-intestinal anastomosis. *J. Urol.* **65**:223-234, 1951.
22. Rich, A. R. On frequency of occurrence of occult carcinoma of prostate. *J. Urol.* **33**:215-223, 1935.
23. Moore, R. A. Morphology of small prostatic carcinoma. *J. Urol.* **33**: 224-234, 1935.
24. Baron, E., and Angrist, A. Incidence of occult adenocarcinoma of prostate after fifty years of age. *Arch. Path.* **32**:787-793, 1941.
25. Huggins, C., and Bergenstal, D. M. Effect of bilateral adrenalectomy on certain human tumors. *Proc. Nat. Acad. Sc.* **38**:73-76, 1952.
26. Harrison, J. H., Thorn, G. W., and Jenkins, D. Unpublished data.
27. West, C. D., Hollander, V. P., Whitmore, W. F., Jr., Randall, H. T., and Pearson, O. H. Effect of bilateral adrenalectomy upon neoplastic disease in man. *Cancer* **5**:1009-1018, 1952.
28. Moore, R. A. Teratoid tumors of testis. *J. Urol.* **65**:693-708, 1951.
29. Lewis, L. G. Radical orchiectomy for tumors of testis. *J. A. M. A.* **137**:828-832, 1948.
30. Cooper, J. F., Leadbetter, W. F., and Chute, R. Thoracoabdominal approach for retroperitoneal gland dissection: its application to testis tumors. *Surg., Gynec. & Obst.* **90**:486-496, 1950.
31. Merren, D. D., Vest, S. A., and Leyston, C. H., Jr. Treatment of malignant tumors of testis. *J. Urol.* **65**:128-135, 1951.
32. Cahill, G. F. Results of surgery in tumor of testis, especially radical removal. *J. Urol.* **66**:280-284, 1951.
33. Committee on Trauma of the American College of Surgeons. *The Early Care of Injuries of the Genito-urinary Tract.* XI: 1-6, 1951.
34. McKay, H. W., Baird, H. H., and Lynch, K. M. Management of injured kidney. *J. A. M. A.* **141**:575-581, 1949.
35. McCague, E. J. Renal trauma: conservative management. *J. Urol.* **63**:773-777, 1950.
36. Prentiss, R. J., and Mullenix, R. B. Management of ureteral injuries in pelvic surgery. *J. A. M. A.* **145**:1244-1248, 1951.
37. MacLean, J. T. Injuries to genitourinary tract. *Canad. M. A. J.* **67**:220-231, 1952.
38. Tempel, C. W. Present status of specific drug treatment of tuberculosis. *J. A. M. A.* **150**:1165-1170, 1952.
39. Carr, D. T. Current status of antimicrobial therapy in tuberculosis. *J. A. M. A.* **150**:1170-1172, 1952.
40. Jacobs, A., and Berthwick, W. M. Streptomycin in urinary tuberculosis. *Proc. Roy. Soc. Med.* **43**:453-466, 1950.
41. Lattimer, J. K., et al. Streptomycin and PAS treatment of genitourinary tuberculosis. *J. Urol.* **67**:750-756, 1952.
42. Galbraith, W. W. Treatment of tuberculosis of urinary tract. *Brit. M. J.* **2**:953-955, 1952.

MEDICAL INTELLIGENCE

VITAMIN A INTOXICATION

Report of a Case in an Adult

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INTOXICATION from overdosage of vitamin A is suggested by the following recognized signs and symptoms: anorexia, irritability, generalized pruritus, painful extremities, arthralgia and sparse, coarse hair.[1] Hepatomegaly and splenomegaly coupled with hypoplastic anemia, clubbing of fingers, and an abnormal appetite for butter and fish oils have been recorded. It is interesting that similar symptoms develop in rats given toxic doses of vitamin A. The fact that until recently vitamin A intoxication has been reported only in infants and children is not surprising; it is this group that receives supplemental vitamin A in a variety of fish oils or concentrates. The conscientious mother may unwittingly overdose her child under the misconception that "if a little is good, a lot is better." The older child may develop a taste for one of the fish oils and overdose himself by overindulging.[1] Mothers using supplemental feeding of vitamin A for their children should be informed of this hazard; the fact that the adult daily requirement of vitamin A[2] is between 2000 and 4000 units, and that of children about half this amount, should be widely publicized.

Vitamin A intoxication, however, is not limited to infants and children. Sulzberger and Lazar[3] recently described this syndrome in an adult who was inspired to self medication with large doses of vitamin A by a radio "nutrition commentator." In its major clinical manifestations the syndrome appears to be the same whether it occurs in children or in adults. During a prolonged course of vitamin A therapy for generalized desquamation, the patient described below manifested the characteristic signs of hypervitaminosis. This case again emphasizes and confirms the opinion of previous authors[2] that "physicians administering large doses of vitamin A must be on the lookout for signs and symptoms of toxicity."

CASE REPORT

Mrs. A. S., a 52-year-old woman, was first seen on February 29, 1952, in consultation at the request of her physician to ascertain the cause of spontaneous bleeding from the mucous membranes.

Since childhood she had had generalized flaking of the skin. About 4½ years previously cracking and oozing about the skin of the legs had developed. When various treatments did not give relief, her physician placed her on a regimen of vitamin A therapy. In the early part of 1948 she received 150,000 international units of vitamin A and 100 mg. of an antihistamine daily for the 1st week and 100,000 units of vitamin A daily thereafter. (The latter dosage of vitamin A was taken from the early part of 1948 until February 29, 1952.) Within 1 month the weeping lesions of the legs cleared, but the desquamation of the skin remained.

In the early part of 1949 she began to suffer from insomnia. By the middle of the same year she felt "out of sorts" and listless but had no specific complaints. Toward the end of the year she noted great difficulty in keeping her hair groomed. In the early part of 1950 she had lost a considerable amount of scalp hair but also noticed loss of hair from the eyebrows and eyelashes, and from the axillary and pubic areas.

By October complete loss of hair from the eyebrows, eyelashes and axillary and pubic areas had occurred. The scalp hair had so thinned that the whole scalp was visible. From then until June, 1951, she began to have stiffness and pain in the joints of the fingers, elbows, shoulders, hips, knees and ankles. At no time, however, did she experience any throbbing, heat or swelling of any joint. Her housework now became too difficult to accomplish. At about this time her husband made the observation that a small patch of skin on the forehead appeared "dirty like" and that his wife's eyes were somewhat more prominent than usual.

Concomitantly with the onset of joint pains, there was a progressive loss of weight and appetite. The patient became completely disinterested in her surroundings and appeared "to brood all the time." Because of a possible relation of pyorrhea to her joint symptoms, she was advised to have all her teeth extracted. Her upper teeth were extracted in June. Extraction was followed by immediate severe hemorrhage and continuous bleeding, even after suture of the gums. However, the surgeon gave vitamin K empirically immediately after operation for a number of injections, after which the bleeding subsided. Thereafter she received a weekly injection of vitamin K and liver from her attending physician. These injections were continued until October.

From June to October she also received a course of cortisone therapy for 12 weeks, without improvement in the joint symptoms. At about this time she began to note severe aching "in the bones" of both upper and lower extremities that was different from the pains in the joints. With the onset of aching in the bones of the extremities, locomotion became impossible because she could not stand for more than a few moments at a time.

In October she was admitted to the hospital for extraction of the lower teeth. Because of the previous history of bleeding after extraction of the upper teeth, she was given empirically an injection of vitamin K preoperatively. Although hemorrhage immediately followed extraction of the teeth, she experienced no further bleeding after suturing of the gums.

By November she had lost over 30 pounds in weight and her appetite was "almost completely gone." At this time her attending physician prescribed 2 vitamin capsules a day. Toward the middle of December she began to note a "thumping headache." By the middle of January, 1952, spontaneous oozing of blood from the nose and a mild irritation of the eyes began. About 3 weeks later the eyes were quite inflamed. At about this time she noted oozing of blood not only from the nose but also from the mucous membrane of the right eye and left external ear canal.

From 1949 to 1951 there had been irregularity of the menstrual periods and occasional bouts of hot flashes. Since March, 1951, there had been no menstrual bleeding.

Physical examination showed the patient to be pale and chronically ill. The scalp hair was coarse, dry and brittle and appeared unkempt, and there was a loss of a great amount of hair. The hair of the eyebrows and eyelashes was completely lacking. Above the glabella there was an area of a few centimeters of light brownish pigmentation. The eyes revealed obvious prominence and pulsation. The conjunctivas demonstrated an ulceroblepharitis, with tear-drop formation of blood from the left. Eyeground examination dis-

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closed abnormal pulsations of the retinal veins, more so on the right than on the left. Oozing of blood was noted from the mucous membranes of the nose and external canal of the right ear. There was a generalized fine desquamation of the skin. The scalp evidenced a moderately severe seborrhea. Axillary hair was completely lacking. Neither the spleen nor the liver was palpable. Pubic hair was also lacking. Vaginal examination was negative except that immediately after examination a generalized oozing of blood was noted from the vaginal mucosa. There was pain on passive or active flexion or extension of any joint. Marked tenderness was elicited over the long bones of all extremities on percussion. None of the joints revealed any swelling or deformity.

At a previous hospital admission on October 26, 1951, the hemoglobin was 11 gm. per 100 cc., and the white-cell count 9400, with a normal differential count. At this time a bleeding time of 2 minutes and a coagulation time of 4½ minutes were found before injection of vitamin K. Examination of the blood on February 29, 1952, showed a red-cell count of 3,500,000, with a hemoglobin of 10.5 gm. per 100 cc., and a white-cell count of 6900, with 3 per cent rod and 47 per cent segmented neutrophils, 6 per cent eosinophils, 1 per cent basophils, 41 per cent lymphocytes and 2 per cent monocytes.

Beginning February 29, 1952, all vitamin therapy was discontinued; and by the end of 1 week the patient volunteered the information that amelioration of symptoms had occurred. The arthralgia and aching in the bones, although present, were improving. The bleeding from the mucous membranes had subsided, and the eyes had cleared. By the end of 5 weeks the aching in the long bones had disappeared, and the arthralgia had considerably improved. She also began to regain her appetite and became more interested in her surroundings. At this time, because of annoying pulsating headaches, she was hospitalized for cerebral angiography. The diagnosis of cerebral aneurysm was not confirmed, and a sternal-marrow puncture was reported as normal except for the presence of marked eosinophilia. She was discharged from the hospital without incident.

Four months later the patient was free of all joint pains and could move all extremities freely. There was a full growth of hair on the eyebrows, eyelashes and pubic area and considerable new growth of scalp hair; the hair of the axillary areas was conspicuously lacking. Six months after her original visit she had regained 30 pounds in weight. She showed the growth of about 12 long hairs in each axilla; hair on the chin and upper lip was also noted. During this time, the pigmentation of the forehead noticed on the first examination had completely disappeared.

At the present writing the bilateral exophthalmos has completely receded. However, a perceptible pulsation of the right eye still persists. On funduscopic examination only the veins in the right eye still reveal marked abnormal pulsations. (Sulzberger and Lazar[3] noted exophthalmos in their patient but questioned its connection with the hypervitaminosis.)

This patient's early symptoms were insomnia and listlessness. It was well over a year before she began to note loss of scalp hair. However, beginning with the history of loss of hair, the symptoms, particularly those referable to the joints, were similar to those of the patient described by Sulzberger and Lazar[3] — except that sweats and generalized pruritus were not experienced. Extraction of the upper teeth exemplified the danger of hemorrhage from the gums and mucous membranes and its correction by administration of vitamin K. The relation of pulsating exophthalmos to vitamin A intoxication, if any, is unknown. The patient never complained of a pulsating headache until a month before vitamin A therapy was stopped; the headaches still persist.

This patient manifested the typical symptomatology; the fact that she was completely relieved of her joint pains and aching bones, with regrowth of lost hair within six months of discontinuation of ingestion of vitamin A, is interpreted as evidence of toxicity of vitamin A ingested in large doses over a prolonged period.

The pathologic processes noted in vitamin A intoxication are the observations recorded from work done on rats. These observations have been summarized in Josephs'[1] article. Rarefaction of bone and thinning of the cortex account for the spontaneous fractures. Although this occurs in the young growing rat under experimental conditions it does not occur in the full-grown animal. An increased excretion of calcium also occurs, but the serum calcium and phosphorus are not affected. In the reticuloendothelial cells, the Kupffer cells of the liver and the spleen an increased deposition of fat is observed. The function of the liver is depressed, and there is a rise in the total lipids. The basal metabolic rate is decreased, but no effect on blood formation is noted in animals.

Swelling and pain of the long bones in the growing infant or child suffering from prolonged overdosage of vitamin A are due to pronounced periosteal thickening.[4] The x-ray appearance of the involved bone may simulate cortical hyperostosis. This does not occur in the adult. Increased total lipid is recorded in human beings. Hypoprothrombinemia and low serum proteins may be explained by liver dysfunction occasioned by increased deposition of fat in the liver. The rise in serum phosphatase that may occur whether implemented by diseased liver or bones is not clearly delineated. The hepatomegaly and splenomegaly may be explained by excess deposition of fat in these organs. Josephs[1] suggests the possibility that pathologic tissue replaced bone marrow to account for the hypoplastic type of anemia that occurred in his case. He also speculates that the occurrence of low basal metabolic rates in these cases is not due to lowered thyroid activity but to the presence of an excess of thyroid antagonist. That a definite relation exists between the thyroid gland and vitamin A is suggested in the summary of the experiment recorded by Sulzberger and Lazar.[3] It has been demonstrated that the simultaneous administration of vitamin A and thyroxin prevents a rise in basal metabolic rate, that administration of a diet high in cod-liver oil to patients with exophthalmic goiter reduces the basal metabolic rate, that persons with hypothyroidism have low vitamin A levels and that in rats vitamin A causes a decrease in thyroid size and reduces the basal metabolic rate. In a clinical description of patients with vitamin A intoxication these authors allude to the great similarity between the

appearance of the skin in hypervitaminosis and that in hypothyroidism, avitaminosis and hypovitaminosis.

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References

1. Josephs, H. W. Hypervitaminosis A or carotenemia. *Am. J. Dis. Child.* **67**:33-43, 1944.
2. Butt, H. R. Fat-soluble vitamins A, E, and K. Council on Foods and Nutrition. *J. A. M. A.* **143**:236-241, 1950.
3. Sulzberger, M. B., and Lazar, M. P. Hypervitaminosis A: report of case in adult. *J. A. M. A.* **146**:788-793, 1951.
4. Toomey, J. A., and Mousette, R. A. Hypervitaminosis A. *Am. J. Dis. Child.* **73**:473-480, 1947.

Additional References

Fried, C. T., and Grand, M. J. H. Hypervitaminosis A. *Am. J. Dis. Child.* **79**:475-486, 1950.

Wyatt, T. C., Carabello, C. A., and Fletcher, M. E. Hypervitaminosis A: report of case. *J. A. M. A.* **144**:304, 1950.

THE PRACTICAL USE OF A COOLING DEVICE TO INHIBIT THE CUTANEOUS PAIN OF HYPODERMIC INJECTIONS*

HARRY L. MUELLER, M.D.†

BOSTON

THE pain, discomfort, unpleasantness and anxiety attendant upon hypodermic injections given to children is well known to most physicians, particularly to those, such as pediatricians and allergists, who routinely administer a large number of hypodermic injections. The fear of anticipation is often much worse than the actual pain of the injection and is frequently translated into unpleasant disturbances in the reception room of the office or on the wards and in the outpatient clinics of the hospital. Extreme examples have been noted in children who start to scream as the car in which they are riding approaches or passes the doctor's office, where they have previously been inoculated. Certainly, some children are so emotionally upset by injections that treatment could be termed "worse than the disease." Although I have had no experience with adults, many of them also have a profound fear of "needles" and are quite uneasy about receiving hypodermic injections.

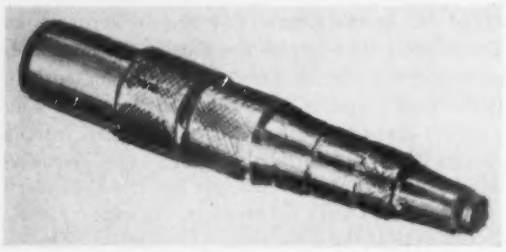

FIGURE 1. *Automatic Freon Gas Refrigerating Unit (Approximately One Fifth Actual Size.)*

With these facts in mind, use of the cooling method for inhibition of cutaneous pain, according to the method of Ingraham, Matson and Woods,‡ after their report in 1947, was begun. Over this period the various cooling devices have included a vacuum-bottle type with ice, ice and calcium chloride, hand-operated freon gas and finally automatic-valve-operated freon gas.

While attempts to determine the value of such an apparatus in practical use were being made, the convenient, efficient and economical unit shown in Figure 1 was devised.§ By means of a cartridge of freon gas, seated by the action of a metal screw cap, a measured amount of the gas automatically flows into a chamber at the tip by pressure of the tip on a firm surface. When this pressure is released the gas is allowed to escape through a small opening and in so doing cools the tip to a temperature of approximately 5°C. in a total time of about five seconds. The smooth metal disk at the tip is then held firmly against the skin for forty-five to sixty seconds, reducing the skin temperature to approximately 11°C. The hypodermic needle is inserted through the cooled skin, counteracting the sensation of needle pressure by counterpressure on the adjacent skin. More than 7000 hypodermic injections have been given by this method, 1800 in the past year. Many of these are multiple injections on the same patient. The ages of the children varied from two to sixteen years. Infants below the age of two years were not included in this study since subjective results from this age group could not be obtained and evaluated. The number of injections that could be given from one gas cartridge varied from 12 to 28, with an average of 22 during the past year. As the operator became familiar with the device and its efficient use, the average number of injections per cartridge increased.

Results

From an entirely practical standpoint the use of a cooling device for inhibition of cutaneous pain in hypodermic injections was eminently successful both for the doctor and for the patient in private office practice. It eliminated almost all the anxiety and unpleasantness for the patients on whom it was employed. Results were fairly uniform, only occasional failures being caused by technical difficulties. In several patients there appeared to be complete failure of inhibition of pain whenever the cooling device was used. These were highly emotional children with a great deal of anxiety and a low pain threshold. These are regarded as failures

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‡Ingraham, F. D., Matson, D. D., and Woods, R. P. Inhibition of cutaneous pain responses by local application of cold: simple method of reducing pain of hypodermic injections. *New Eng. J. Med.* **237**:773-776, 1947.

§Developed with the technical assistance of Dr. Frederick Keyes and his associates and Mr. Robert Fish, of Alfred Bicknell Associates, Cambridge, Massachusetts.

to obtain the child's confidence, since in 1 case when confidence finally was established the child agreed that there was no longer any pain with injection after cooling.

I discovered that when the apparatus was first used it was better to describe the process to the child before bringing the cooling device into view; otherwise he might immediately interpret the device as a method of giving an injection and the cooler itself then appeared more formidable than a syringe. This was particularly true with the earlier vacuum-bottle model, which was large and made of shiny aluminum, but occurred less frequently with the later, small gas models. Children under three years of age were more difficult to initiate into its use, but became avid "fans" after they learned that it actually made the injection painless.

The cooling period of approximately a minute lengthens the actual time required for the administration of an inoculation, but this may be more apparent than real because with a willing, relaxed patient no time is lost in coaxing, forcing or jockeying in and out of position, as it is with an apprehensive child about to receive an injection. In addition, the mother may be taught to hold the cooler while the operator is preparing the solution to be injected.

The process was useful, in many cases, to introduce and condition older children for a series of injections. Once started they gradually gained courage to reject the cooler and displayed a certain pride in having the injections without it. That the device is successful in inhibiting cutaneous pain is confirmed by the fact that some of these patients went back to its use, obviously preferring comfort to bravery.

A final byproduct of usefulness was the effect on the parent. Many mothers suffer acutely when their children receive injections, and if they allow this suffering to become apparent, it serves to increase the difficulty with the child. It was found that injections given after the use of a cooling device had an additional salutary effect upon the parent, to the benefit of all.

As reported by Ingraham et al. cooling did not inhibit the pain of intradermal injections although it did inhibit the pain associated with introduction of the needle. Furthermore, with subcutaneous or intramuscular injections, there may be some pain or discomfort from the actual injection of the material, depending on the amount and type of the substance injected.

CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL

Weekly Clinicopathological Exercises

FOUNDED BY RICHARD C. CABOT

BENJAMIN CASTLEMAN, M.D., *Editor*

VIRGINIA W. TOWNE, *Assistant Editor*

CASE 39161

PRESENTATION OF CASE

First admission. A sixty-nine-year-old widow was admitted to the hospital for study.

The patient had been in reasonably good health except for mild arthritis of the hips and knees until seven weeks before admission, when she noted a great deal of gas in the abdomen, with excessive belching and passage of flatus. This was associated with an aching pain in the midback under each scapula, radiating to the epigastrium and relieved somewhat by passage of gas. There was no history of selective food intolerance, nausea, vomiting, change in bowel habits or weight loss. The remainder of the past history was noncontributory.

Physical examination revealed a slightly overweight, apprehensive woman, whose chief concern was that she might have cancer. The lungs were clear to percussion and auscultation. The heart borders were within normal limits, and there was a Grade 2 precordial systolic murmur. Examination of the abdomen was negative. There were mild crepitus of the knee joints and Heberden's nodes of the fingers; otherwise, the physical examination was negative.

The temperature was 98.6°F., the pulse 50, and the respirations 16. The blood pressure was 140 systolic, 80 diastolic.

The urine was normal. Examination of the blood showed a hemoglobin of 13.4 gm. per 100 cc. and a white-cell count of 9100, with 66 per cent neutrophils, 25 per cent lymphocytes and 9 per cent monocytes. The sedimentation rate was 14, 25, 34 and 40 mm. at fifteen-minute intervals. The stool guaiac test was negative. The alkaline phosphatase was 3.8 units per 100 cc., the blood lipase 0.04 cc. (normal, under 2 cc.), and the bromsulfalein retention 4 per cent. X-ray examination of the upper gastrointestinal tract was negative except for a small hiatus hernia; a barium-enema examination showed diverticulosis of the sigmoid colon but no inflammatory change. A Graham test of the gall bladder was negative.

Final admission (seven weeks later). After discharge from the hospital the patient seemed well for six weeks, but then noted an increase in pain under both scapulas, radiating to the epigastrium and associated with slight nausea, and mild pressure pain in the chest, the last related to stair climbing. She had been taking her own temperature and had noted a daily evening rise to 100 to 101°F.

Physical examination revealed an extremely agitated and distraught woman, with a coarse tremor of the extended fingers. The skin was dry. Except for a firm, nontender subcutaneous nodule measuring 1 cm. in diameter in the abdominal wall just to the left of the umbilicus the examination was unchanged.

The temperature was 101.4°F., the pulse 90, and the respirations 16. The blood pressure was 135 systolic, 90 diastolic.

The urine had a specific gravity of 1.016 and gave a + test for albumin. The urine urobilinogen was

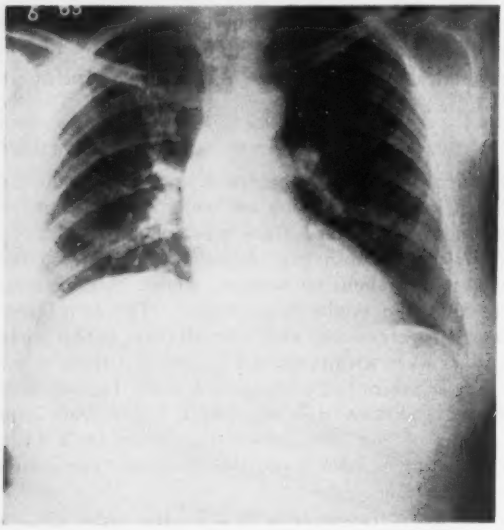

FIGURE 1.

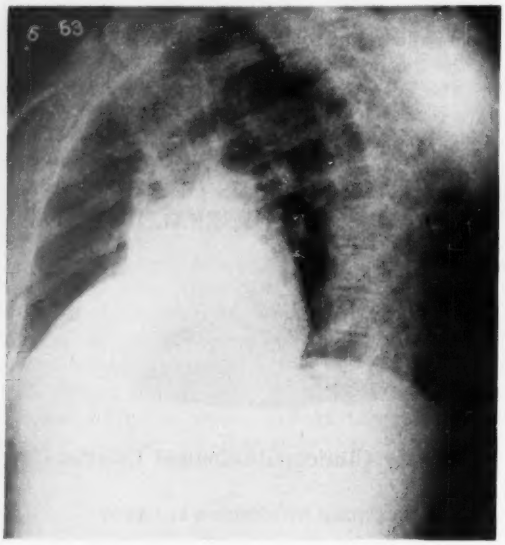

FIGURE 2.

4.2 Ehrlich units (normal, 1.0 Ehrlich units). Examination of the blood showed a hemoglobin of 9.8 gm., per 100 cc. and a white-cell count of 9700, with 79 per cent neutrophils, 12 per cent lymphocytes, 7 per cent monocytes and 2 per cent eosinophils. The sedimentation rate was 32, 51, 58 and 60 mm. at quarter-hour intervals. The total protein was 5.7 gm., the albumin 3.6 gm., the globulin 2.1 gm., the serum bilirubin 0.2 mg. direct, 0.5 mg. total, the serum calcium 9.0 mg., the phosphorus 4.1 mg., the alkaline phosphatase 3.7 Bodansky units, and the serum amylase 10 units per 100 cc.; the serum lipase was 0.01 cc. The bromsulfalein retention was 26 per cent, the cephalin flocculation + in forty-eight hours, and the thymol turbidity negative. The prothrombin time was 14 seconds (normal, 13 seconds). A Coombs test was negative. A stool was guaiac negative and negative for ova and parasites. Two blood cultures were negative. Agglutinations for typhoid, paratyphoid and brucella were negative. An electrocardiogram demonstrated normal rhythm with slight sagging of the ST segments in Leads 1 and AVL and prominent Q waves in Leads 3 and AVF; the precordial leads showed upright R waves, with a normal sequence, but with abnormally low T waves across the chest. Roentgenograms of the chest disclosed clear lung fields, though the right leaf of the diaphragm was elevated in its anterior half, with a large, rounded shadow beneath the diaphragm (Fig. 1 and 2). The heart shadow was quite prominent in the region of the left ventricle, and the aorta was tortuous. No bone destruction was noted in the spine, though there was minimal displacement of the fourth lumbar vertebra in relation to the fifth and a suggestion of a slight fusiform widening of the abdominal aorta. An intravenous pyelogram showed normal kidneys; no stones were seen; the excretion time was normal. The ureters and psoas-muscle shadows were normal.

During her hospital course the patient progressively weakened despite blood transfusions and other supportive measures. She continued to be afebrile in the morning and to have daily spikes of temperature to 101°F. in the evening. The white-cell count increased to 14,200, with 84 per cent mature and 2 per cent young neutrophils, 13 per cent lymphocytes and 1 per cent eosinophils. The liver

became palpably enlarged, the edge extending four fingerbreadths below the costal margin. Another bromsulfalein test showed 36 per cent retention of the dye. The abdominal subcutaneous nodule appeared to have become larger. On the tenth hospital day an operation was performed.

Differential Diagnosis

Dr. John B. Stanbury*: "A Graham test of the gall bladder was negative." Does that mean that the gall bladder filled well with dye?

Dr. Stanley M. Wyman: That is correct.

Dr. Stanbury: "The liver became palpably enlarged, the edge extending four fingerbreadths below the costal margin." Was the liver not palpable when she came in for the second admission and palpable ten days later?

Dr. Robert H. Fennell, Jr.: It is stated in the admission physical examination that the liver was not palpable.

Dr. Warren Point: It was certainly enlarged on the tenth day; I cannot vouch for its size on the first day.

Dr. Stanbury: I shall have to accept it as it stands.

The obvious fact that emerges from this protocol is that the patient had liver disease. Almost everything else in the protocol is secondary to or concomitant with the liver disease. My task is to try to ascertain the nature of the pathologic process in the liver. She had a disease that, from the first symptom to operation, occupied approximately four months. During this time the clinical and laboratory signs of hepatic disease, including an enlarged liver and bromsulfalein retention, developed. I should like to suggest the various types of liver disease that could conceivably give this picture, and to choose one that might most reasonably be the diagnosis.

In the first place, I can dismiss certain types of liver disease that are such remote possibilities that they do not deserve attention. Among these is acute hepatitis. The negative flocculation tests and the absence of jaundice rule out this diagnosis. There was nothing to suggest that she had acute infectious hepatitis, nor was there anything to suggest cirrhosis except the slightly low blood protein and the bromsulfalein retention. Neither could the enlargement of the liver and its contour be explained on the basis of congestive heart failure. Nothing in the protocol except the slight enlargement of the heart and the electrocardiographic changes suggested that she was in congestive heart failure.

I think, therefore, that I can confine the discussion to acute pyogenic infection and to neoplastic disease of the liver. Liver abscess does not seem like a reasonable possibility. The patient had fever, to be sure, but there were no chills, and the white-cell count was not nearly so high as one finds with acute hepatic abscess; there was no portal of entry. Without further consideration I should like to dismiss liver abscess and go on to a consideration of neoplastic disease of the liver. This might be an appropriate time to look at the x-ray films. The Service was obviously concerned about a possible site of origin of the disease, and examined practically every area of the body by x-ray.

Dr. Wyman: I have selected a few representative films from the many examinations. The gall bladder contains dense dye, and no stones are present.

Dr. Stanbury: Is the common duct entirely negative? You do not see any pressure on the gall bladder?

Dr. Wyman: No; there is nothing to suggest extrinsic pressure. The gastrointestinal series shows a hiatus hernia, a rather common finding to which I should attach no especial significance. The duodenal cap and loop are not remarkable. The stomach is not displaced, nor does it show any intrinsic abnormality. There is a considerable amount of calcification in the abdominal aorta, but that is not surprising at this patient's age. The kidneys, which are quite well visualized, seem normal in size and shape. There is a calcification in the pelvis that I think is in an old fibroid. The colon on the post-evacuation film shows a few small diverticula but nothing else to suggest intrinsic disease.

Dr. Stanbury: Did you get a good look at the ascending colon and cecum?

Dr. Wyman: Yes; I am quite sure it is normal. The prominence of the right leaf of the diaphragm is adequately seen (Fig. 1 and 2). It is smooth, rounded and quite large. I do not think one can say what is causing this. Fluoroscopically, there was one finding that is not present in the protocol — that is, the rounded portion of the diaphragm did not contract normally and remained in its position of elevation throughout the fluoroscopic procedure, whereas the surrounding portion of the diaphragm contracted well.

Dr. Stanbury: Is there any fluid in the chest?

Dr. Wyman: There is no fluid in the chest, and the lung fields are clear. The heart is slightly prominent in the region of the left ventricle and the aorta is tortuous, but I think this is in keeping with an arteriosclerotic aorta.

Dr. Stanbury: What about the bone defect?

Dr. Wyman: I think that is an incidental finding and not important; I should not pay too much attention to it.

Dr. Stanbury: Obviously there are only two kinds of neoplastic disease that have to be considered: primary and secondary. I do not think a diagnosis of hepatoma can be established in this patient. Her pain could have been the sort that may be encountered in hepatoma. The observation in the x-ray films of a large single mass in the liver, with secondary masses elsewhere, is suggestive of

*Assistant physician, Massachusetts General Hospital.

a primary neoplasm in that area, with the rest of the liver secondarily involved. The absence of any suggestion of pre-existing liver disease is strong evidence against hepatoma.

The possibility of carcinoma of the bile ducts must certainly be entertained, but when this disease is present it often manifests itself in the same way that gallstones do — by the presence of jaundice — and often suggests an acute attack of cholecystitis with obstruction in the biliary tree. There is no such history, and I am unable, in view of the negative Graham test, to make a diagnosis of carcinoma of the bile duct.

This leaves me with secondary carcinoma of the liver. Where would the primary site have been? One can list any number of possible organs of origin, and for each there is contrary evidence. One might consider the stomach, for instance. If the liver grew as fast as I am told it grew, it is entirely consistent with metastases from carcinoma of the stomach, for such metastases to the liver grow as fast as or faster than those from any other organ of the body. Furthermore, the periumbilical mass, which I assume was a metastatic nodule, can arise from practically any viscus, but most commonly it comes from carcinoma of the stomach. However, it is difficult to make this diagnosis in the face of a negative gastrointestinal series and a negative stool guaiac reaction. This brings up a side issue, — the hemoglobin, which declined by about 4 gm. per 100 cc. in the course of seven weeks, and yet there was no evidence of blood loss. Possibly the blood loss was intermittent, and the several guaiac tests failed to pick it up.

What about the lung? There is no evidence that the patient had carcinoma of the lung. The chest film is perfectly satisfactory. What other site should be considered? The pancreas? Carcinoma of the body and tail of the pancreas can be an exceedingly silent disease manifested only by pain. In most recent series it has been stated that pain is the commonest introductory symptom for carcinoma of the pancreas. The pain usually bores through, straight to the back. This patient's pain was higher in the subscapular area and was bandlike. The rapid progression of anemia is against carcinoma of the pancreas; such patients can maintain their hemoglobin very well for quite a long time. The periumbilical node is consistent with carcinoma of the body or tail of the pancreas, and the mild nausea that this patient exhibited is often encountered in carcinoma of the pancreas. The mechanism is totally unexplained.

There are numerous other organs from which metastatic disease may have come. One is the ovary, from which there may be a periumbilical node. Another is the small bowel, but there was no x-ray evidence of cancer there and cancer of the small bowel is an extremely rare disease. Another important area is the large bowel. Large-bowel neoplasms may be extremely small at a time when there is massive metastatic neoplastic disease in the liver. The local bowel neoplasm may easily be missed by x-ray examination. In spite of an adequate examination I cannot completely dismiss a small primary neoplasm in the ascending colon or cecum with metastases to the liver.

There are two additional points that I should like to mention: the fever and the elevated sedimentation rate are entirely consistent with metastatic carcinoma of the liver — in fact, they are routine findings. In passing I should also mention the substernal pain that the patient complained of. That, coupled with the electrocardiographic findings, indicates mild arteriosclerotic heart disease and angina pectoris.

I cannot arrive at a logical diagnosis. I cannot make a diagnosis of carcinoma of the lung with a normal chest roentgenogram; I cannot make a logical diagnosis of carcinoma of the stomach with a negative stool guaiac reaction and a negative gastrointestinal series; I cannot make a logical diagnosis of carcinoma of the large bowel with two negative barium-enema examinations and the negative guaiac test on the stool; I cannot make a logical diagnosis of carcinoma of the kidneys with a negative intravenous pyelogram (they usually metastasize to the lungs and bones anyway); I cannot make a logical diagnosis of carcinoma of the bile ducts or gall bladder in the absence of jaundice and in the presence of a negative Graham test; I cannot make a logical diagnosis of carcinoma of the ovary with a negative pelvic examination; and I cannot make a logical diagnosis of carcinoma of the pancreas in the absence of a mass.

It all boils down to this: I am fairly confident in making a diagnosis of metastatic disease to the liver, but I cannot make a logical diagnosis of the site of origin of the carcinoma except by elimination. My guess is that the primary tumor was in the body or tail of the pancreas. My supposition is that the operation referred to in the protocol was a biopsy of the periumbilical mass. Probably, the patient subsequently died, and the site of origin of the tumor was then found. If I had to make a second guess, I should say that a carcinoma of the stomach was overlooked in the gastrointestinal series.

Dr. Gordon S. Myers: Was this woman a native of the United States?

Dr. Myles P. Baker: Yes; she had lived all her life in this country. The abnormal right leaf of the diaphragm raised the question of amebic infection in the liver. The right-upper-quadrant and subscapular pain and the fever in the presence of a normal white-cell count, which she had before and at the time of admission, are an unusual combination in amebic abscess of the liver. We did pursue this diagnosis and sent a stool for examination, which was reported negative for *Endamoeba histolytica.*

The clinical picture is well given in the protocol. The patient had complained of subscapular pain for five months — pain that was unexplained by x-ray examination done two months before death — without definite evidence of liver disease or pancreatic disease at that time. In reviewing the gastrointestinal series done about two months before admission, the radiologist noted the high right leaf of the diaphragm, but its significance was not appreciated by me. The patient remained active despite her distress, which she minimized, and only sought further medical advice when she realized that she had an evening fever.

DR. FENNELL: The operation was a liver biopsy done by Dr. Point, who will tell us about it.

DR. POINT: The biopsy was very easy to do. When the needle was first inserted, I felt that I was going through soft mush with no consistence whatsoever; the tissue throughout the rest of the needle's course felt normal. When I withdrew the needle it was quite obvious that I had entered two different kinds of tissue; the first was homogeneous mucoid material that held its shape, and below it was apparently normal liver tissue.

CLINICAL DIAGNOSIS

?Cirrhosis, with hepatoma.
?Metastatic carcinoma of liver, from unknown primary source.

DR. JOHN B. STANBURY'S DIAGNOSIS

Carcinoma of body or tail of pancreas, with metastases to liver.

ANATOMICAL DIAGNOSES

Undifferentiated carcinoma of tail of pancreas, with extension to stomach and splenic vein, and with metastases to liver, periumbilical subcutaneous tissue and regional lymph nodes.
Cholangitis, acute.
(Jaundice.)
Pulmonary emboli, with pulmonary infarction.
Thrombosis of posterior tibial veins, bilateral.
Marantic thrombi, aortic valve.

PATHOLOGICAL DISCUSSION

DR. FENNELL: The biopsy did show that there was a poorly differentiated carcinoma in the liver. We thought it was probably metastatic, but could not rule out the possibility of hepatoma. The patient's condition continued to deteriorate, and she had daily elevations of temperature to 102°F., but repeated blood cultures were negative. The jaundice increased, and she died nine days after the biopsy was done.

At autopsy we found a carcinoma arising in the tail of the pancreas. It was a large (8-cm.), hard nodular mass that had extended to the stomach and had involved the splenic vein, with thrombosis of the vein and focal infarction in the spleen. There were widespread and extensive lymph-node metastases; the nodule that was palpable adjacent to the umbilicus was a mass of tumor. The nodes in the porta hepatis and around the bile duct were quite large, some up to 2 cm. in diameter, and they encroached upon but did not invade the bile ducts, which did not seem to be dilated. Numerous masses of tumor were present in the liver, and much of the tumor was hemorrhagic and necrotic.

Microscopically, the tumor was poorly differentiated, but in some areas it formed intercellular bridges and tended to keratinize and resembled a squamous-cell carcinoma; I suppose one might call it a Grade 4, squamous-cell carcinoma. The liver showed marked bile stasis, with a large amount of cholangitis and pericholangitis. Because the picture was uniform throughout the liver I think there was some obstruction to the bile duct. One would not expect such uniform widespread change merely from scattered masses of intrahepatic tumor.

There were massive pulmonary emboli; one was lodged in the left lower lobe, where there was an infarct that was a few days old. I think the emboli were the precipitating cause of death. She had thrombi in both posterior tibial veins, which I am sure were the site of origin of the emboli. I suppose this could be listed as another case in which there was a tendency to peripheral thrombosis associated with carcinoma of the body and tail of the pancreas although we find this particular site of origin of thrombi very commonly in patients who do not have this disease.

There were fairly large vegetations, 0.5 cm. or so in size, on the two coronary cusps of the aortic valve, but they were the marantic type of thrombi from the microscopical appearance. There were no bacteria and almost no inflammatory cells present in them. It would be helpful to explain the fever that this patient had on the basis of a bacterial endocarditis, but I am sure this was not a bacterial endocarditis.

DR. BAKER: One of the extraordinary features of this case was that the patient's husband died, three years before she did, with carcinoma of the pancreas; it was a diagnosis particularly in her mind, and we could not help thinking of it too. Two things that I should remember from a diagnostic point of view are the elevation of the right leaf of the diaphragm and the fact that during the period of study for the first and only time over a period of several years, she had a rapid sedimentation rate. I think this is one case in which an elevated sedimentation rate really meant something.

DR. STANBURY: Do you put any stock in the personality changes that are said to be found in patients with carcinoma of the pancreas?

DR. BAKER: I do not believe they are specific for this disease. In such patients without jaundice, pain develops without explanation by x-ray examination. These may seem to be plausible reasons

for seeking a psychiatrist's help, only to have later a laparotomy or post-mortem examination disclose the diagnosis. In this particular case the patient was extremely worried, and rightly so.

DR. FENNELL: We did not examine the brain so that I cannot tell whether or not there were metastases to it.

DR. WYMAN: I should like to say one thing about the right side of the diaphragm. It was extremely important in this case. We have an old film from a previous examination that makes this perfectly apparent. I should like to add a word of warning, however: a diaphragm similar to or identical with this may be seen in normal persons with a lobulated liver so that this must not be taken too seriously in many films.

DR. BENJAMIN CASTLEMAN: Is that the finding that Dr. Schatzki* reported as being seen in some patients with hepatoma?

DR. WYMAN: Yes; we considered that a possibility, but we did not have any evidence of splenic enlargement or esophageal varices to suggest cirrhosis.

*Schatzki, R. Roentgenological diagnosis of primary carcinoma of liver. *Am. J. Roentgenol.* 46:476-483, 1941.

CASE 39162

PRESENTATION OF CASE

A sixty-three-year-old man was admitted to the hospital because of a mass in the lung.

During the six months before admission the patient had become fatigued easily and felt more tired than usual. About four weeks before admission a "virus attack," characterized chiefly by a hacking cough, which was productive of a slight amount of mucoid material, developed. This did not contain blood, nor did it appear to be purulent. He also had a slight wheezing but no sore throat or nasal discharge. He thought he had a fever for two or three days, and was treated with penicillin daily for a week. At this time a roentgenogram of the chest was said to have demonstrated a "spot" in the right lung. Two weeks later a second roentgenogram showed the density to be still present. During the two weeks before admission the symptoms subsided except for an occasional episode of wheezing, tightness and coughing for five or ten minutes. On occasion, more often upon arising, he coughed up white phlegm.

Four years before admission he had pneumonia in the right lung and was treated at home with penicillin for two or three weeks. This apparently healed completely, and he did not have a residual cough. He did not smoke and had not had any known contact with tuberculosis. He had not had night sweats or chills. He had lost 8 pounds in weight during the past six months.

Physical examination showed a moderately obese man who did not appear ill. There was no clubbing of the fingers. The heart and lungs were normal. The remainder of the examination was negative.

The temperature was 98.8°F., the pulse 90, and the respirations 20. The blood pressure was 160 systolic, 90 diastolic.

The urine had a specific gravity of 1.010 and was normal except for the sediment, which contained 3 white cells and a rare hyaline cast per high-power field. Examination of the blood revealed a hemoglobin of 16.0 gm. and a white-cell count of 9800, with 81 per cent mature and 2 per cent young

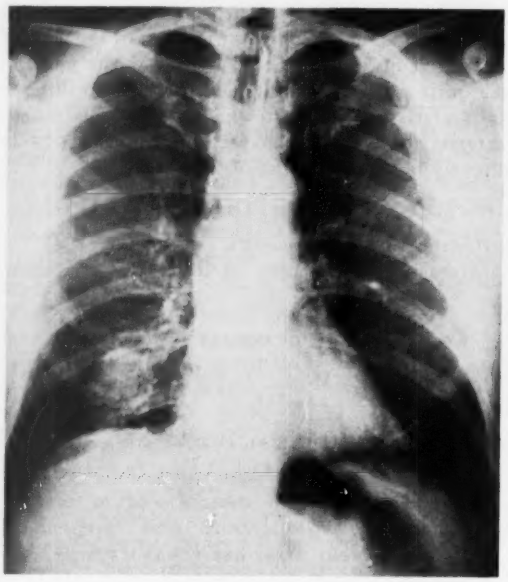

FIGURE 1.

neutrophils, 15 per cent lymphocytes and 2 per cent monocytes. A sputum examination was negative for tumor cells and bacteria. A roentgenogram of the chest disclosed a roughly spherical lobulated homogeneous density measuring 4 cm. in diameter lying within the medial basal portion of the right lower lobe (Fig. 1 and 2). The lung was otherwise clear, and there was no definite evidence of lymphadenopathy. An intravenous pyelogram showed the kidney outlines, particularly in their upper portions, to be partially obscured by intestinal gas. The kidneys were not definitely enlarged, and the contrast substance was excreted promptly by both kidneys, outlining nondilated ureters.

Bronchoscopy demonstrated a normal trachea; the carina was sharp and movable. The right

bronchial tree was thoroughly inspected, and no endobronchial lesion was observed. The terminal bronchi were all identified. The left bronchial tree was likewise normal. Saline solution was introduced into the right-lower-lobe bronchus and aspirated for cytologic examination, which was subsequently reported as negative.

On the fifth hospital day an operation was performed.

Differential Diagnosis

Dr. Rita M. Kelley*: In summary, this sixty-three-year-old man was found on a routine chest

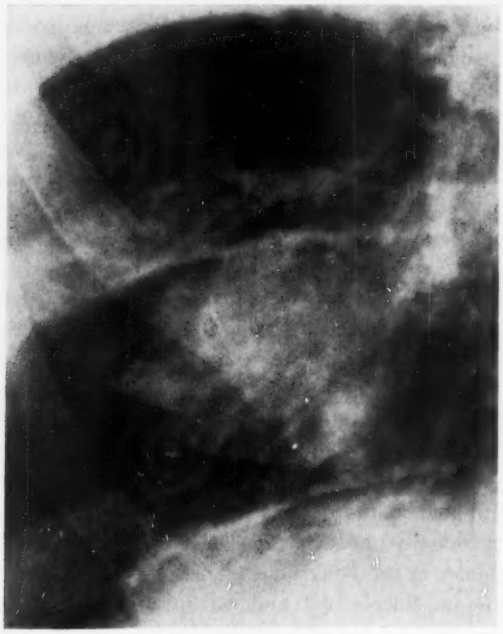

Figure 2.

x-ray examination for a not unusual type of respiratory infection to have a mass in the lung. May I see the films?

Dr. Joseph Hanelin: There is an isolated, 4-cm., rounded mass within the medial basilar portion of the right lower lobe (Fig. 1). There is no evidence of atelectasis of this portion of the lung, and the lungs otherwise appear quite clear. There is likewise no indication of adenopathy either at the lung roots or in the mediastinum. I think the spot film outlines the mass to best advantage (Fig. 2). The heart is of normal size. Two films from the pyelographic examination appear quite normal.

Dr. Kelley: Was the patient fluoroscoped at this time and nothing unusual noted?

*Assistant in medicine, Massachusetts General Hospital.

Dr. Hanelin: Yes; he was fluoroscoped. No process, other than the mass, no obvious collapse of the adjoining lung and no pleural effusion were noted.

Dr. Kelley: This lesion appears to have occurred in a perfectly normal man except for the vague symptoms that preceded its development. It is tempting to try to relate the presence of the lesion to the pneumonia of the right lung that he had four years previously. I think, however, that the lateralization of the pneumonia was sheer coincidence, because if he had an endobronchial lesion four years before admission that was large enough to cause obstruction, with the development of pneumonia behind the obstruction, he would be unlikely to have been completely free of all symptoms for four years. I assume that an x-ray examination was not made at that time since the pneumonia was treated at home. Since the patient had been entirely devoid of symptoms, the earlier pneumonia probably had nothing to do with the present lesion.

There is a suspicion, however, that the more recent respiratory difficulty may have been related to the lesion. Yet the description of the vague virus attack is not unlike what many of us in practice have recently been seeing with great frequency; the only odd feature that suggests some relation of that to the previous lesion was the fact that the patient wheezed. There was no indication of any lateralization of the wheeze, but it is possible that there was temporary partial blockage of the bronchus, perhaps on the basis of edema, leading to a mild infection accompanied by some wheezing, which persisted even after the other symptoms subsided. The residual spasmodic cough and a slight production of phlegm in the morning have been very common with the virus attacks that we are currently calling grippe or "flu" to hide our ignorance of its specific nature. So it is quite possible that this recent attack of respiratory infection had little to do with the presence of the lesion itself and that it was an unexpected finding on the x-ray film. I am somewhat supported in this by the bronchoscopic report. I understand from the bronchoscopists that the bronchi that serve the medial basal segment of the right lower lobe are easily visualized; since they were well visualized, if a lesion had been encroaching on the lumen of the bronchus it would certainly have been found. I think, therefore, that this lesion was extrinsic to the bronchial lumen.

What kind of pulmonary lesion occurs in a man of sixty-three? The odds are overwhelmingly in favor of a malignant lesion in this age group. The easy fatigability and slight weight loss that he had noted for the six months preceding admission may have represented the first insidious manifestations of the malignant process before it had become large enough or invasive enough to produce any specific symptoms. Those symptoms, however, were vague and not spectacular and may have had nothing

whatever to do with the presence of this lesion. If this was a malignant lesion, the chances are that it was a bronchogenic carcinoma since that is the most common type of malignant lesion in the lungs. The x-ray picture is very much against this diagnosis; bronchogenic carcinoma presenting as a sharply defined limited mass like this, without any evidence of reaction around it, is very unusual. Again, the negative bronchoscopic report is against bronchogenic carcinoma since these lesions arise within the bronchial lumen and not outside it. That the sputum and bronchial washings were negative for tumor cells supports the supposition that this was not a bronchogenic carcinoma but, of course, does not rule it out. Even though a bronchogenic carcinoma was not large enough to be visualized in the bronchoscope, one might expect to find tumor cells in the sputum or bronchial washings.

Another kind of malignant lesion that this could have been is a primary sarcoma of the lung. Although very rare such lesions have been described as being extrabronchial, intrapulmonary and sharply localized as a rule. If I were to place this first on the list as a diagnostic possibility, it would only be in tribute to the high premium that esoterica hold in this type of conference; otherwise, I have no ground on which to call this a primary sarcoma although I cannot rule it out.

The third type of malignant lesion that could conceivably have caused this picture is lymphoma. A solitary lymphoma in this part of the lung would be unusual, and there was no sign of involvement of the mediastinum. I gather that there was no evidence of peripheral lymphadenopathy. The patient had an excellent hemoglobin and nothing to support a positive diagnosis of lymphoma.

Having talked myself out of all the primary lesions that this could have been, I now turn to the possible metastatic lesion that could have caused this picture. Solitary metastatic nodules of this size in the lungs are rare; metastatic lesions are usually multiple by the time they assume these proportions. However, one tumor that can give rise to a solitary nodule like this is the hypernephroma. That it was considered a real diagnostic possibility was indicated by the fact that the Service did an intravenous pyelogram although the urine was not remarkable. A negative intravenous pyelogram is against hypernephroma, but it does not rule it out entirely since a small primary lesion can set up a large solitary metastasis. I have no other way of ruling out a single metastatic nodule from a hypernephroma than I have of ruling out a sarcoma except on the basis of the extreme rarity of these lesions. Since it is a rare lesion anyway, it would be rarer with a negative intravenous pyelogram.

Despite this man's age I am now faced with the problem of selecting a benign lesion that could have caused this picture. At this point I have to abandon any attempt at an analytical approach because numerous types of benign lesions can be present, as well defined lobulated masses without any distinguishing characteristics whatever. They are all rare lesions. It is merely a toss of a coin to decide which one it may have been so I shall mention the possible ones and pick one at random. Because there was no evidence of involvement of or connection with the mediastinum, this is unlikely to have been a teratoma, dermoid or neurofibroma, all of which usually originate in or at least demonstrate some connection with the mediastinum. A tuberculoma could appear in this region and give this picture, but there was nothing to make me suspect previous tuberculosis in this man and no evidence on which to base such a diagnosis. Chondromas can arise in the bronchial cartilage. It could also have been an osteoma or a fibroma in this area although those lesions are especially rare. Hemangiomas, although they commonly cause symptoms and are often multiple rather than single or at least are associated with angiomatous lesions elsewhere in the body, can occasionally present as isolated, asymptomatic nodules in the x-ray films. These lesions often pulsate on fluoroscopy and on special x-ray views demonstrate vascular connections with the hilar vessels. There was no definite evidence of angioma, but I cannot rule it out.

Possibly the most common type of benign tumor in and around the bronchus is a bronchial adenoma. These lesions usually present in the lumen of the bronchus, however, rather than extrinsic to it and usually manifest themselves by definite evidence of obstruction. Adenomas have occasionally been described that were primarily extrabronchial or peribronchial. The case under discussion could conceivably fall into that pattern.

Finally, a lesion known as a hamartoma, which is not really a tumor, is according to at least one author more common in the pulmonary structures than the bronchial adenoma. The hamartoma is

more or less an abnormality in growth in which the normal tissues of the organ are present in a large mass that is not frankly tumor. Many people believe that the chondroma, the angioma and some of these other tumors are really hamartomas, with one particular type of local structure predominating.

Faced with a choice of one of these types, I shall choose a benign lesion rather than a malignant one, and, on the basis of probability, I shall say that it was an adenoma or a hamartoma. I shall give as a second choice primary sarcoma and as a very poor third metastatic hypernephroma.

Dr. Hanelin: One thing that I might mention about solitary lesions of the lung, which we frequently see as the result of survey films, is that they often prove to be primary carcinomas even though there is not much reaction around the lesion or visible evidence of adenopathy.

Clinical Diagnosis

Carcinoma of right lower lobe.

Dr. Rita M. Kelley's Diagnosis

Benign tumor of right lower lobe, ?adenoma, ?hamartoma.

Anatomical Diagnosis

Adenoma of bronchus, carcinoid type.

Pathological Discussion

Dr. Benjamin Castleman: During exploration Dr. Edward D. Churchill, who operated on this patient, felt a large mass that he thought was about 4 cm. in diameter in the medial basal segment of the right lower lobe. He resected the entire lower lobe and handed it to one of the pathologists. In the operating room when the pathologist cut through the lobe, pus exuded from a multiloculated cavity, which looked like an abscess. The question then arose whether it was really an abscess or perhaps a bronchogenic cyst because it was lined with thinned-out bronchial mucosa. At that time two bronchi were found leading to this cystic mass, which replaced the entire medial basal segment of the lobe. Just above the bifurcation of these two bronchi was a small anthracotic lymph node that we believed had perhaps produced enough pressure to obstruct and cause inspissation and bronchiectasis. When we examined the specimen more carefully in the laboratory, however, we found a nubbin inside the bronchus extending out from this node suggesting that it may have been broncholith. This nubbin, which measured 4 or 5 mm. in diameter, proved microscopically to be a bronchial adenoma of the carcinoid type, made up of small uniform cells. The patient had almost certainly had the adenoma for a long time, and the incident four years before admission was probably related to it.

The New England Journal of Medicine

Official Organ of
THE MASSACHUSETTS MEDICAL SOCIETY
and
THE NEW HAMPSHIRE MEDICAL SOCIETY
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THE DOCTOR DRAFT LAW

LETTERS published elsewhere in this issue of the *Journal* call attention to one particular source of discontent with the current so-called "doctor draft" law, which expires on July 1, 1953. This dissatisfaction is based on the unfairness of recalling for a full two-year term of service those veterans who happen to have served a moment less than the twenty-one months that constituted the requirement of their original call to duty. According to the requirements of the present law, any young man who happened to have served twenty-one months on his original call is placed in a less vulnerable priority whereas his classmate, who happened to have received his discharge a day earlier, is subject now to recall for a complete two-year stretch.

Other provisions of this unsatisfactory act, which has caused so much controversy, have received due attention — largely as a result of the tenacity of purpose of the American Medical Association — and it is hoped that a new and better law may be enacted to replace the present one, or that the present one, if re-enacted, will be wholesomely amended. Service in the armed forces of a cobelligerent nation, for example, should be recognized; adequate provisions should be made for the most effective proportion of medical to other personnel in order that an excessive number of physicians should not be drawn into service to their own detriment and that of the civil population, and provision should be made against the improper use of medical officers, whether in nonmedical activities or in caring for nonmilitary personnel.

In such ways the physicians of the nation find that they need protection against what they believe to be unfair and unnecessary military exploitation. So long as this exists to any degree they can hardly be criticized for a reluctance to flock voluntarily to the colors. The doctor draft law itself, requiring of a special group compulsory military service to an age twenty years beyond that of any other persons, represents, of course, discriminatory legislation however necessary it may be and however cheerfully accepted as necessary by those on whom it falls.

Unfortunately, the often heated expressions of opinion on this subject, both within and outside the medical profession, have caused a question to arise in the minds of the public at large: Do American doctors and their leaders wish that the present principle of special treatment be continued, with both the special considerations and the special liabilities and responsibilities now imposed on them, and, if so, with what modifications? It should be recognized that, except for the maximum induction age, the hardships and inequities of the present law fall on physician and layman alike, requirements of twenty-one months' prior service and obligations arising from previous A.S.T.P. and V12 training applying to both. The young doctor who perforce gives up his residency or newly established practice to begin training for Army medical service suffers

no more, to some ways of thinking, than the young engineer, architect or lawyer who begins training for the duties of rifleman, bombardier or yeoman first class.

The bill proposed by the Department of Defense, as outlined in the March 13 letter of the Secretary of the American Medical Association, goes far to correct the inequities of the present law; indeed, in waiving current limitations on the number of commissions of higher grades so far as physicians are concerned, it would specifically favor the medical components of the armed forces.

Perhaps the answer is that the physician confronted with the prospect of military duty desires no special consideration in requirements or conditions of service that is not given his fellow citizens in nonmedical fields. And perhaps the sole justifiable limitation on the selection and assignment of medical officers consists in the provision of adequate medical care for the civilian population and the stipulation that the precious training and experience that qualify a man for medical practice will not be wasted in duplication of duties and unnecessary assignments in the military service. The good of his patient and his country has not ceased to be the primary consideration of every physician — even one faced with a tour of duty in the armed forces.

EUROPEAN HEALTH COMMUNITY

A "European Health Community," proposed by the French government, was the subject of discussion at a meeting held in Paris last December, according to an annotation in the December 27 issue of the *Lancet*. The plan, as introduced by the French minister of public health and population was predicated "on the assumption that certain supranational powers should be given to a new health organization representing a Community of those European nations wishing to join."

The proposals fall into two groups. The first consists of such obligations or restrictions laid upon all members of the Community as "the abolition of customs dues on pharmaceutical products or medical appliances, and the abolition of unfair competitive practices in these fields." The second comprises such common tasks and objectives as "the pooling of medical products and facilities and the results of research, as well as uniformity in social-security legislation." These objectives, it is believed, might lead to the establishment of laboratories and research centers for the study of common problems of health and disease.

The British government emphatically declared itself as opposed to the granting of any "supranational powers," although interested in an association with the Community on terms that would not prejudice any of Britain's national rights.

If the establishment of an international organization along any such lines is seriously contemplated, convincing proof should be offered that its proposed functions could not be as well performed by such existing bodies as the World Health Organization with its Regional Organization for Europe, the Brussels Treaty Organization or the Council of Europe.

In any event, the proposals are to be examined by a committee of experts and reported back to the conference this year.

AMERICAN ACADEMY OF PEDIATRICS

The *Journal*, in common with many other historic Boston institutions and the numerous hotels of the city, extends a cordial welcome to the members of the American Academy of Pediatrics, who will gather at the Hotel Statler on April 20, 21 and 22, 1953.

This meeting, the first to be held by the Academy in Boston in eleven years is also the first areal meeting of the organization to be held in this city. Even as pediatrics, one learns, has no especial reference to feet, so areal, it transpires, has little if anything to do with aviation.

The three days of the meeting will be adequately filled with scientific sessions, clinics and visits to local points of interest. Those attending the banquet will have the privilege of hearing Dr. Benjamin M. Spock, professor of child development, University of Pittsburgh School of Medicine, who will talk on "The Pediatrician's Family."

BOOM TOWN, CONNECTICUT

THE dean of Yale University School of Medicine has announced the receipt of two substantial gifts and the consummation of the purpose for which a third considerable sum of money was granted.

From the Commonwealth Fund the Connecticut university has obtained a grant of $2,500,000 for construction of a residence hall for medical students to be designated as the Edward S. Harkness Memorial Hall. This dormitory, if it may be so called, will be located adjacent to the Sterling Hall of Medicine and the Grace–New Haven Community Hospital and will include rooms for single and married students, suites for visiting scientists, a lounge, a dining hall and recreation rooms.

A gift of $6,000,000 has been received from the Social Research Foundation for the establishment of a fund for research in psychiatry. The fund will provide assistance to other universities as well as to Yale for basic research in psychiatry and related behavioral sciences. The board of directors, under the chairmanship of Dr. Frederick C. Redlich, Yale professor of psychiatry, will include Dr. Vernon W. Lippard, dean of Yale University School of Medicine, Dr. Charles D. Aring, of the University of Cincinnati, Dr. John Benjamin, of the University of Colorado, Dr. David Shakow, of the University of Illinois, Dr. George W. Thorn, of Harvard, and Dr. John C. Whitehorn, of Johns Hopkins.

The Memorial Unit of the Grace–New Haven Community Hospital was completed and dedicated in February. This up-to-date unit, increasing the potential bed capacity of the hospital to 805 was constructed at a cost of approximately $9,000,000. It includes facilities for 327 patients, a nurses' home and laundry and dietary facilities for the entire hospital.

Medical education, despite its astronomical costs, appears not to be faltering in New Haven.

A "medium" being lately consulted as to the character of the disease of which a person had died, spelled out consumption; *but it turned out that he was blown up in a steamboat.*

Boston M. & S. J., *April 20, 1853*

MASSACHUSETTS MEDICAL SOCIETY

HAVE YOU PAID YOUR DUES?

The annual session of the American Medical Association will be held in New York City June 1 to June 5. The headquarters, scientific and technical exhibits, and other meetings will be at the Grand Central Palace, 44th Street and Lexington Avenue.

To avoid the usual congestion at the registration windows and to save trouble and delay, the American Medical Association is issuing advance-registration cards, which will make it possible for those who wish to attend to register quickly instead of waiting in line to have their records checked with the membership roster.

To register, it is necessary to have a pocket card showing membership dues in the American Medical Association paid for 1953. Members who have not already sent in checks to cover 1953 dues are urged to do so at once, so as to give the Society an opportunity to forward the payment to the American Medical Association in time to have the Association issue a pocket card and also an advance-registration card.

MASSACHUSETTS DEPARTMENT OF PUBLIC HEALTH

HUMAN SERUM ALBUMIN

Human serum albumin has been distributed on special order by the Department through the Biologic Laboratories of the Institute of Laboratories since December, 1946. This product, as well as immune serum globulin, is obtained from outdated blood. Thus, it is essential that all outdated whole blood be saved for this purpose.

The policy on the distribution of albumin has been controlled by a committee consisting of Drs. Charles A. Janeway, Francis D. Moore and William C. Moloney. Physicians have been requested to call the Laboratory and discuss the case briefly with the doctor charged with its distribution. A report by the doctor is requested on each case.

Some of the clinical considerations influencing the decision whether or not to use the albumin in specific cases have been as follows: its osmotic effect in drawing water from the tissues into the circulation, restoring blood volume; its value in restoring the blood level of albumin — for example, in the correction of low blood protein levels preoperatively, and in the stimulation of wound heal-

ing, especially the prevention and treatment of wound lysis, occurring postoperatively; the danger of further renal damage in certain types of kidney lesions; the tendency to produce right-sided heart failure from a sudden increase in blood volume; and the danger of rupture of esophageal varices in alcoholic cirrhosis and the poor results in patients with prolonged ascites.

Many clinicians believe that if beneficial results are not manifest by the time 200 to 250 gm. are given, it is useless or may even be dangerous to push the use of albumin farther. Because of the high cost and low supply of albumin, it should not be used in merely any type of extreme case in the hope that it will be of value.

The following is a list of conditions in which it has seemed of most value: acute liver conditions associated with low blood protein; kidney disease with edema; the preparation of poor-risk patients for operation; obstruction of the bowel from edema; nontropical sprue; and generalized anasarca due to low serum proteins.

Letters should be directed to the Biologic Laboratories, 375 South Street, Jamaica Plain 30, Massachusetts (telephone, JA 2-3700).

CORRESPONDENCE

PRIORITY III DRAFT CALL

To the Editor: I am in receipt of a letter from Senator Saltonstall dated March 23, 1953, in which he states that it is his understanding that no physicians over the age of thirty-six will be called up in the Priority III draft. If this is so, it seems to me the fact should be made known for the benefit of those concerned with mortgage contracts, insurance estate, leases and so forth.

DANIEL J. BELL, M.D.

Cambridge, Massachusetts

COMMENTS ON THE DOCTOR DRAFT

To the Editor: I am venturing to offer a protest against the current basis for recalling to military service doctors who received their medical education during the war years under the Army Student Training Program and then served as medical officers until they were mustered out. Those who served less than twenty-one months may be called back to serve an additional two years. The obvious injustice of this plan is that a few days over or under twenty-one months makes the difference between exemption and a two-year extension of service. This seems to me an exorbitant demand. I object to the premise that these men owe extra service because their medical training was subsidized. They cheerfully accepted the disadvantages and hardships of acceleration and then served as long as they were needed. The financial component of the arrangement seems to me irrelevant. We should not regard them as medical mercenaries. In my view the over-all term of service for draft-eligible physicians should be the same regardless of their priority classification by Selective Service. If this equitable basis does not provide enough doctors, as apparently it will not, a reasonable adjustment would be a uniform extension of required service. An addition of six or eight months would probably suffice, and the evident unfairness of asking the ASTP group to bear the brunt of covering the deficit would be avoided. We should be as considerate of this group who have already served us as we possibly can be. We are obliged to ask further service of them, but I feel very strongly that they should not be "selectively" exploited.

Boston JAMES L. GAMBLE, M.D.

To the Editor: I should like to point out what appears to me to be gross injustices in the present doctors' draft law:

At present doctors in Priority II with one day less than twenty-one months' service are being recalled to serve for seventeen to twenty-four months — that is essentially as long as those who have had no previous service. This in effect makes a total service of just under forty-five months for this group, whereas all others are now asked to serve approximately half as long. Obviously, there is a minimum period during which a medical officer can be used efficiently by the services, but certainly for a person with previous service this must be somewhere between six and twelve months. A graded length of service dependent on previous service would more equitably answer the problem and spread the burden of military service more evenly and justly. Thus persons in my own situation (four days short of twenty-one months) would be expected to serve one and a half times as long as others, not twice as long. Giving credit for previous service would only mean that more doctors in Priority III without a day of service would be expected to serve, an eventuality that does not seem unjust. With 33,000 doctors in this group, the needs of the Army can easily be met.

It also seems unjust that doctors who were strongly urged by the armed forces and the medical schools to stay in medical school and join ASTP or V-12 (as an essential part of the war effort) during the last war should now be penalized for having done so. Naturally, they have, like all others, an obligation to serve in the armed forces, but is this obligation greater than that of persons who were deferred for teaching, research or practice and gained in many cases, tremendously financially or academically thereby? The present law suggests that those in Priorities I and II should be punished for having stayed in medical school and forces double service on many of them before Priority III doctors serve a day.

I should like to suggest that others who believe that the present law is unjust in these or other respects make a strong effort to have the new law made more equitable. Previously, the doctors actually affected by the law have been totally unrepresented at any of the Congressional hearings, and moves should be made to correct this when the law comes up for revision in the near future.

CHARLES D. COOK, M.D.

Boston

To the Editor: There are several inequities in the so-called "doctors' draft law" that should be brought to the attention of the readers. Most of these inequities fall directly on those doctors in Group II. However, members of the profession in Group IV, to whom the law is now only a vague unpleasantness, will be similarly affected in the future. I shall bring up only two points, which to me are extremely unfair, although others, such as lack of recognition of service with a cobelligerent country, are equally important.

The first point is lack of credit for previous service. A man in Group II who has served all but one day of the required twenty-one months now can be recalled for an additional two years, thereby serving a total of forty-five months minus one day. On the other hand, doctors in Group I or Group III, who have had no previous service, are eligible for discharge and have fulfilled their military obligations at the end of twenty-four months.

The second point I wish to make is that of physical requirements. There are definite standards for all military personnel except physicians. A doctor who is able to practice with a static disability and who has a normal life expectancy should be required to serve if he has not already done so. However, there are cases in which doctors are called or recalled with chronic progressive diseases such as diabetes and hypertension. They would not be accepted in any other branch of the service, and if their disease is aggravated by active duty, they will be a permanent burden to the taxpayer. It is perfectly true that they can practice now and may be able to for some time to come, but two years out of their limited earning span is a disproportionate sacrifice to both themselves and their families.

WILLIAM C. WIGGLESWORTH, M.D.

Ipswich, Massachusetts

To the Editor: Shortly, the doctor's draft law (Public Law 779, 81st Congress) is due to expire. This law was rapidly conceived in a time of emergency, and as such unavoidably contains many gross inequities. However, a new law is about to be drawn up, and it is of the utmost importance that those doctors affected by this law suggest improvements to and solicit support of their senators and congressmen before this enactment takes place.

Under present legislation, previous service of nonmedical veterans, Group I and Group II veterans, is not recognized. A physician in Group II who may lack one or two days of the required twenty-one months' minimum is expected to serve an additional twenty-four months, or a total of forty-four to forty-five months. This is, in many cases, almost twice the time requirement of Group III, or those without any prior service.

A proposal before Congress at the present time would attempt in part to equalize this, by limiting the second call for these veterans. Those with twelve months to twenty months and twenty-nine days of previous service would now be recalled for a duty period of seventeen months. This is a step in the right direction, but is not sufficient. A more graded scale of service is needed. A more equitable solution would be a graded period or recall, perhaps on a basis of three-month increments, depending on the amount of previous duty.

Recent surveys of the available physician supply indicate that there is a large source of doctors without previous service. It seems only fair that they be called for a first tour of duty before the others be called for double service.

Boston GEORGE E. LACROIX, M.D.

GRANDPA DRAFT

To the Editor: As is generally known Congress is at present considering in committee a revision of the doctor draft law. Although there are many details that should be corrected, as with any complex law, I should like to call attention to a basic inequity existing in the present law. The administrative divisions of all doctors under fifty-one years of age are under review by Congress, and the possible regroupings proposed will determine whether or not doctors in Category III, as now defined, will ever see any military duty. This category includes approximately 33,000 doctors who were deferred from active duty during World War II by virtue of civilian health needs, by the requirements of medical-school faculties and by the exacting health standards for screening doctors for military duty during the "hot" war. *Deferment* does not mean *exemption*, and only a minor portion of this deferred group assumed inconveniences, hazards, or responsibilities remotely equivalent to the chance fortunes of the doctors in uniform. A mere handful of this same group continues to hold irreplaceable posts. Should we not extend to this group an early opportunity for experience in the armed forces?

Age and physical limitations are often stated as a barrier to useful service, but we all recall many men over fifty years of age who contributed their share and more in the war. The health standards have been reduced in an accommodating manner, and since most doctors in the armed forces claim that the duties are not so arduous as those of their civilian practice, it is clear that age and health are not the barriers to active duty they once were considered.

Not uncommonly the question of leaving a home life and dependents is raised as a legitimate reason for exemption of senior doctors from service, but this attitude ignores the fact that many doctors of a similar age did just this during the war.

Finally, it is claimed that the older and more experienced doctors would not possibly be given medical responsibilities equivalent to those that they have in civilian life. The fact that the services cannot fully utilize a doctor's talents is hardly a logical cause for deferment because to accept this as a valid reason for deferment is to swallow the proposition that lawyers, chemists, architects and artists should have been deferred in World War II, since their civilian skills would not be 100 per cent realized in their military duty.

It is naturally too much to ask of this group that they volunteer, since we live in an age in which central authorities are established to control the efficient use of manpower. If reform is needed, let all doctors stand up and be counted and urge their congressmen to redress the wrong! Only by the maximum distribution of military duties throughout the medical profession can a reasonable individual tour of duty be achieved. All within the widest possible limits must share this military obligation.

BENJAMIN A. BARNES, M.D.

New York, New York

MISCELLANY

JOURNAL DE GÉNÉTIQUE HUMAINE

Journal de génétique humaine, the first periodical in French devoted to human genetics recently appeared. It is intended for all physicians, biologists, anthropologists and others interested in the study of heredity in man. The committee of editors is composed of three leading physicians and geneticists: Professor A. Franceschetti, director of the University Ophthalmological Clinic, Geneva; professor L. Van Bogaert, director of the Neuro-Pathological Department of the Institute Bunge, Antwerp; and Maurice Lamy, professor of human genetics of the Medical Faculty, Paris. The journal will appear four times a year.

BOOKS RECEIVED

The receipt of the following books is acknowledged, and this listing must be regarded as a sufficient return for the courtesy of the sender. Books that appear to be of particular interest will be reviewed as space permits. Additional information in regard to all listed books will be gladly furnished on request.

Blutgruppenbestimmung und Bluttransfusion. By Dr. Med. Habil. Peter Dahr, professor, Universität Göttingen and governor, Institut für Blutgruppenforschung Göttingen; and Ob.-Med.-Rat Dr. E. Regenbogen, physician-in-chief, med. Klinik Abt. A Städt. Krankenanstalten Osnabrück. Second edition. 8°, cloth, 256 pp., with 16 illustrations. Stuttgart: Georg Thieme, 1952. Ganzleinen DM 16.50. (Distributed by Grune and Stratton, New York.)

This monograph on the determination of blood groups and on blood transfusion is written in two parts. The first, by Dr. Dahr, discusses untoward effects and their avoidance. The second, by Dr. Regenbogen, is devoted to technic, indications and contraindications. The material has been brought up to date since the publication of the first edition in 1950. There is a bibliography and a good index. The publishing is excellent. The book is recommended for collections on the subject.

Projective Test Productions. I. Projective Drawings. By Claire M. Vernier, Ph.D., chief clinical psychologist, Veterans Administration Center, Martinsburg, West Virginia, and lecturer and research consultant, The Catholic University of America. With a foreword by Isabelle V. Kendig, Ph.D., chief psychologist, Veterans Administration Hospital, Tomah, Wisconsin. 4°, paper, 168 pp., with 60 illustrations. New York: Grune and Stratton, 1952. $6.00.

This book is an album of pictures, with descriptive text, drawn by persons afflicted with mental disorders and psychoneuroses, including schizophrenia, manic-depressive, involutional and other psychoses, mental deficiency and examples of psychopathic conditions, with and without psychosis. There is a bibliography of eighty-four references and a good index. The book should prove of value to psychiatrists and psychologists.

A Text-book of Pathology. By E. T. Bell, M.D. Contributors: B. J. Clawson, M.D., and J. S. McCartney, M.D., professor of pathology, University of Minnesota Medical School. Seventh edition. 8°, cloth, 1008 pp., with 529 illustrations and 5 color plates. Philadelphia: Lea and Febiger, 1952. $12.00.

This standard textbook has been thoroughly revised and brought up to date. A large part of the text has been rewritten, and much material has been added. The book has been written primarily for students but is valuable as a reference work on the subject. Lists of references are appended to the chapters, and there is an extensive index. The publishing is excellent.

Urological Pathology. By Peter A. Herbut, M.D., professor of pathology, Jefferson Medical College, and director of Clinical Laboratories, Jefferson Medical College Hospital, Philadelphia. In two volumes. 8°, cloth. Vol. 1, 693 pp., with 298 illustrations. Vol. 2, 527 pp., with 227 illustrations. Philadelphia: Lea and Febiger, 1952. $24.00 for the set.

In writing this new treatise the author has reviewed the literature of the past twenty to twenty-five years. The material is arranged on a regional basis of the organs of the male genitourinary tract. Extensive bibliographies are appended to the chapters. There is a comprehensive index; the illustrations and publishing in general are excellent. The book is recommended for all collections on urology.

Studies on Testis and Ovary Eggs and Sperm: Proceedings of a conference sponsored by the Committee on Human Reproduction, National Research Council, in behalf of the National Committee on Maternal Health, Inc. Edited by Earl T. Engle. 8°, cloth, 237 pp., with 95 illustrations. Springfield, Illinois: Charles C Thomas, 1952. $7.50.

The conference was devoted to a discussion of various aspects of the physiology of reproduction. Fourteen papers were read by 17 persons on spermatogenesis, spermatozoa and sperm activity; fertility; the ovary, the ovum and ovarian function; the Sertoli cell; allenolic acid; and semi-sterility in man and animals. There were 79 members of the conference, a number of whom discussed the papers. Lists of references are appended to the various papers. Publications of this type have a definite reference value and as a class should be in all medical libraries.

Figure della medicina contemporanea italiana. By Giovanni P. Arcieri, docente di storia della medicina. 8°, cloth, 352 pp., with 23 portraits. Milan: Fratelli Bocca Editori, 1952. $6.00. (Distributed by S. F. Vanni, 30 West 12th Street, New York City.)

Dr. Arcieri, of New York, has brought together biographies of 23 well known modern Italian physicians. A good portrait accompanies each biography. These doctors have made notable contributions to medical science, in various fields. Among the names may be mentioned Banti, Forlanini, Golgi, Grassi, Maragliano, Putti and Sanarelli. A valuable appendix lists the complete writings of all the physicians noted. The text is written in easy Italian, and the publishing is excellent. The book is recommended for all medical-history collections.

Culdoscopy: A new technic in gynecologic and obstetric diagnosis. By Albert Decker, M.D., D.O.G., clinical professor of gynecology and obstetrics, New York Polyclinic Medical School and Hospital, associate attending physician in gynecology and obstetrics, New York Polyclinic Hospital, and attending gynecologist, Knickerbocker Hospital. With a foreword by Richard W. TeLinde, M.D. 8°, cloth, 148 pp., with 50 illustrations. Philadelphia: W. B. Saunders Company, 1952. $3.50. (*American Monograph Series.*)

In this monograph Dr. Decker has summarized his large experience in the use of his culdoscope in visualization of the pelvic viscera. The beginning chapters present the history and development of culdoscopy, the anatomy of the vagina, a description of the Decker culdoscope and the technic of its use. These are followed by chapters on colpoceliocentesis, ectopic pregnancy, sterility, uterotubal insufflation, pneumoperitoneum, endometriosis and ovulation and ovum transfer. The text concludes with a discussion of endoscopic photography, case reports and a bibliography. The monograph should be available in collections on gynecology and obstetrics.

Outlines of Internal Medicine. Edited by C. J. Watson, M.D., head, department of medicine, University of Minnesota. Seventh edition. 4°, cloth, 601 pp., with illustrations. Dubuque, Iowa: William C. Brown Company, 1952. $13.00.

This new edition of a standard book on internal medicine has been revised and brought up to date. The text has been divided into five parts: infectious diseases and related conditions; diseases of the blood and digestive system; diseases of the heart and circulatory system; deficiency and endocrine diseases and diabetes mellitus; and clinical chemistry and microscopy. The book is the joint effort of 24 members and former members of the staff of the University of Minnesota. The material has been useful, and the outlines should prove valuable to the practicing physician for ready reference.

Reaction to Injury: Pathology for students of disease. Volume II. *The Reactions of Submission and Adaptation and the Disease Entities Arising out of their Elaboration.* By Wiley D. Forbus, M.D., professor of pathology, Duke University School of Medicine, and pathologist to the Duke Hospital. 4°, cloth, 1110 pp., with 836 illustrations. Baltimore: Williams and Wilkins, 1952. $20.00.

The first volume of this extensive treatise was published late in 1943. The present volume discusses, in its third section, the submission to injury and the pathologic entities arising therefrom — disturbances in metabolism and function of the endocrine glands and of the process of growth and development with and without structural alteration of the tissues. The fourth section considers the reaction to injury through functional and structural adaptation, sometimes consisting of compensatory reactions of cells, tissues and organ systems after injury. Lists of references are appended to the various chapters, and there is a good index of subjects. The set should be in all collections on pathology.

NONCLINICAL NOTES

NEW DEAN AT ROCHESTER

Dr. Donald G. Anderson, secretary of the Council on Medical Education and Hospitals of the American Medical Association and secretary-treasurer of the American Medical Education Foundation, has been appointed dean of the University of Rochester School of Medicine and Dentistry.

Dr. Anderson, a fellow of the Massachusetts Medical Society, was formerly dean of Boston University School of Medicine.

BRONZE MEDAL

Dr. Charles C. Lund, of Boston, has been awarded the Bronze Medal of the American Cancer Society.

NOTICES

THIRD INTERNATIONAL CONGRESS OF ELECTROENCEPHALOGRAPHY AND CLINICAL NEUROPHYSIOLOGY

The third International Congress of Electroencephalography and clinical neurophysiology will be held in Boston, August 18-21. The program will include general symposiums on such subjects as epilepsy and other nervous and mental diseases, individual lectures, panels and exhibits.

The American branch of the League against Epilepsy will meet in Boston at the same time.

Further particulars regarding the Congress may be obtained from the Secretary General, Dr. Robert S. Schwab, Massachusetts General Hospital, Boston.

BOSTON UNIVERSITY CHAPTER OF ALPHA OMEGA ALPHA

On Monday, April 27, the Boston University Chapter of Alpha Omega Alpha will sponsor its second lecture of the current year. At 5 p.m. in the auditorium of Boston University School of Medicine, 80 East Concord Street, Dr. Alexander B. Gutman, professor of medicine, Columbia University College of Physicians and Surgeons, and director of medical research, Mount Sinai Hospital, New York City, will speak on the subject "Recent Advances of Purine Metabolism and their Relation to the Pathogenesis of Gout."

This address is open to the medical profession. A hearty welcome is extended to all.

VALLEYHEAD HOSPITAL

The annual meeting of Valleyhead Hospital will be held at the hospital, 20 South Street, Carlisle, Massachusetts, on Thursday, April 23, at 7 p.m. This meeting is held in connection with the fifth anniversary of the founding of the hospital.

The Most Reverend John J. Wright, D.D., Bishop of Worcester, will speak on the subject "Psychiatry and Spiritual Values." A general discussion will follow, and a buffet supper will be served.

Interested physicians are cordially invited to attend.

AMERICAN ASSOCIATION OF GENITO-URINARY SURGEONS

The sixty-fourth annual meeting of the American Association of Genito-Urinary Surgeons will be held at The Homestead, Hot Springs, Virginia, on Wednesday, Thursday and Friday, May 6, 7, and 8. The program will include lectures, symposiums, a business meeting and a formal banquet.

SOCIETY MEETINGS AND CONFERENCES

April 17–27. Consultation Clinics for Crippled Children in Massachusetts. Page 523, issue of March 19.
April 19–24. National Industrial Health Conference. Page 308, issue of February 12.
April 20–22. American Academy of Pediatrics. Page 664, issue of April 9.
April 21. South End Medical Club. Page 570, issue of March 26.
April 21, 23 and 28. Edward K. Dunham Lectures. Page 663, issue of April 9.
April 22. New England Society of Psychiatry. Page 664, issue of April 9.
April 22. Middlesex South District Medical Society. Page 620, issue of April 2.
April 23. Valleyhead Hospital. Annual Meeting. Notice above.
April 24–29. American College of Allergists. Page 570, issue of March 26.
April 25. Boston City Hospital Alumni Association. Page 570, issue of March 26.
April 25. Alumni Association of the State University College of Medicine at New York City. Page 396, issue of February 26.
April 25. Graduate Club of Boston. Phi Delta Epsilon Medical Fraternity. Page 307, issue of February 12.
April 27. Boston University Chapter of Alpha Omega Alpha. Page 707.
April 27 and May 4. Massachusetts Department of Mental Health. Postgraduate Seminar in Neurology and Psychiatry. Page 540, issue of October 2.
April 28. Hampden District Medical Society. Page 663, issue of April 9.
April 29 and October 28. New England Obstetrical and Gynecological Society. Page 868, issue of November 27.
May 2. When Is the Treatment of Mitral Stenosis Surgical? Drs. Laurence B. Ellis and Dwight E. Harken. Mount Auburn Hospital, Cambridge. 10:05 a.m.
May 6. Cutter Lecture on Preventive Medicine. Page 663, issue of April 9.
May 6–8. American Association of Genito-Urinary Surgeons. Notice above.
May 7–9. American Goiter Association. Page 480, issue of March 12.
May 11–13. Aero Medical Association. Page 526, issue of March 19.
May 18–22. National Tuberculosis Association. Page 664, issue of April 9.
May 19–21. Massachusetts Medical Society. Hotel Statler, Boston.
May 20. Massachusetts School Physicians' Association. Page 663, issue of April 9.
May 25–31. First World Congress on Fertility and Sterility. Page 1001, issue of December 18.
May 30 and 31. Society for Investigative Dermatology, Inc. Page 570, issue of March 26.
June 7–9. American College of Cardiology. Page 395, issue of February 26.
June 26–28. American Academy of Dental Medicine. Page 664, issue of April 9.
June 28–July 2. American Society of X-Ray Technicians. Page 480, issue of March 12.
July 8 and 9. Seventh Annual Rocky Mountain Cancer Conference. Page 644, issue of April 9.
August 18–21. Third International Congress of Electroencephalography and Clinical Neurophysiology. Page 707.

District Medical Societies

ESSEX NORTH

May 13. Andover Country Club, Shawsheen.

HAMPDEN

April 28. Rovelli's, Springfield, 6:30 p.m.

MIDDLESEX SOUTH

April 22.

WORCESTER

May 6. Annual Meeting. Sheraton Hotel. Dr. Louis H. Bauer, President, American Medical Association.

Calendar of Boston District for the Week Beginning Thursday, April 23

Thursday, April 23

*8:30–10:00 a.m. Orthopedic Staff Conference. Boston City Hospital.
*9:00–10:00 a.m. Arthritis Grand Rounds. Robert Breck Brigham Hospital.
9:00–10:00 a.m. Grand Rounds. Russell Room, House of the Good Samaritan.
*11:00 a.m.–12:00 m. Pediatric Conference. Mount Auburn Hospital, Cambridge.
*11:00 a.m.–12:30 p.m. Hand Clinic (Physical Medicine and Rehabilitation Service). Boston City Hospital.
*12:00 m.–1:00 p.m. The Problem of Gastric Ulcer. Dr. Sara M. Jordan. Stearns Auditorium, New England Center Hospital.
5:00 p.m. Edward K. Dunham Lecture. Man During Physical Activity. Dr. Alberto Hurtado. Building D, Harvard Medical School.
*5:00–6:00 p.m. Surgical Division Meeting. Mount Auburn Hospital, Cambridge.

Friday, April 24

*10:00 a.m. Tuberculosis Surgical Clinic. South End Health Unit, 57 East Concord Street.
*10:00 a.m.–1:00 p.m. Medical and Surgical Grand Rounds. Drs. George W. Thorn and Francis D. Moore. Main Amphitheater, Peter Bent Brigham Hospital.
*10:30–11:15 a.m. Diabetes Lecture. Dr. Elliott Joslin. New England Deaconess Hospital.
*10:30 a.m.–1:30 p.m. Combined Medical and Surgical Rounds. Stearns Auditorium, New England Center Hospital.
*1:30 p.m. Fertility and Endocrine Clinic. Free Hospital for Women, Brookline.
*1:30 p.m. Tumor Clinic. Mount Auburn Hospital, Cambridge.
*2:00–3:00 p.m. Pulmonary Conference. Drs. Kane, Ettsten, Woods and others. Stearns Auditorium, New England Center Hospital.
*4:00–6:00 p.m. X-ray Conference. Drs. Sosman and Wittenborg. Stearns Auditorium, New England Center Hospital.
*4:00–10:00 p.m. Alcoholism Clinic. By appointment. Washingtonian Hospital, 41 Waltham Street.

Saturday, April 25

*9:00 a.m. Proctology Clinic. Peter Bent Brigham Hospital.
*9:00 a.m. Alcoholism Clinic. Peter Bent Brigham Hospital.
*11:00 a.m.–12:00 m. Blood Clinic. Dr. William Dameshek. Stearns Auditorium, New England Center Hospital.

Monday, April 27

*8:00–9:00 a.m. Combined Medical and Surgical Rounds for Diabetic Surgery Cases. New England Deaconess Hospital.
*8:30–9:30 a.m. Clinic by entire Surgical Staff and Anesthesia Staff. Cheever Amphitheater, Dowling Building, Boston City Hospital.
*12:00 m.–1:00 p.m. Hematology Conference. Dr. Dameshek, Stearns Auditorium, New England Center Hospital.
*12:15–1:15 p.m. Clinicopathological Conference. Main Amphitheater, Peter Bent Brigham Hospital.
*2:00–8:30 p.m. Postgraduate Seminar in Neurology and Psychiatry. Metropolitan State Hospital, Waltham.
5:00 p.m. Boston University Chapter of Alpha Omega Alpha. Dr. Alexander B. Gutman. Boston University School of Medicine, 80 East Concord Street.
5:15 p.m. Staff Meeting. Harris Hall, New England Deaconess Hospital.
*7:00–9:00 p.m. Anesthesia Teaching Conference. Stearns Auditorium, New England Center Hospital.

Tuesday, April 28

*9:00 a.m. Geriatrics Clinic. Peter Bent Brigham Hospital.
*12:00 m.–1:00 p.m. Regular Grand Rounds of the Pediatric Department. Dowling Amphitheater, Boston City Hospital.
*12:00 m.–1:00 p.m. Tumor Clinic. Dr. H. E. MacMahon. Pratt Diagnostic Clinic, New England Center Hospital.
*12:00 m.–1:00 p.m. Pediatric Rounds. Burnham Memorial Hospital for Children, Massachusetts General Hospital.
*12:15–1:15 p.m. X-ray Conference. Dr. Merrill Sosman. Main Amphitheater, Peter Bent Brigham Hospital.
5:00 p.m. Surgical Journal Review. Mount Auburn Hospital, Cambridge.
5:00 p.m. Edward K. Dunham Lecture. General Physiological and Clinical Considerations. Dr. Alberto Hurtado. Building D, Harvard Medical School.
*5:00–6:00 p.m. Service Meeting followed by Clinical Conference (Medical, Surgical, Obstetrical). Faulkner Hospital.

Wednesday, April 29

*11:00 a.m.–12:00 m. Pediatric Grand Rounds. (Children's Medical Center.) Jimmy Fund Building, 25 Binney Street.
*12:00 m. Boston State Hospital Psychiatric Seminar. Reception Building Auditorium, 591 Morton Street, Dorchester.
*12:00 m.–1:00 p.m. Clinicopathological Conference. (Children's Medical Center.) Jimmy Fund Building, 25 Binney Street.
*12:00 m.–1:00 p.m. The Reversibility of Cellular Determination: Its Role in the Phenomena of Regeneration and Neoplasm. Dr. Weststone. Stearns Auditorium, New England Center Hospital.
12:30 p.m. Weekly Pathological Meeting. Joslin Amphitheater, New England Deaconess Hospital.
12:30–1:30 p.m. Weekly Staff Review of Autopsies. Dr. William A. Meissner. Joslin Auditorium, New England Deaconess Hospital.
*2:00–3:00 p.m. Pediatric Conference for Practitioners. (Children's Medical Center.) Jimmy Fund Building, 25 Binney Street.
4:00 p.m. Thoracic Conference. Held by Overholt Clinic. Harris Hall, New England Deaconess Hospital.
*4:00–5:30 p.m. Fracture Lecture. Boston City Hospital.
7:30 p.m. Lahey Clinic Lecture. Syphilis. Dr. Carlton R. Souders. Skin Disease. Dr. John L. Fromer. Joslin Auditorium, New England Deaconess Hospital.

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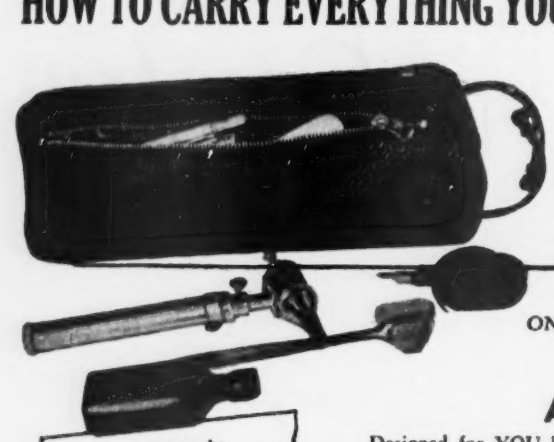

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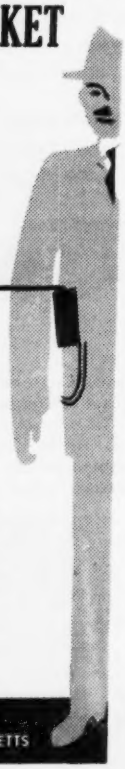

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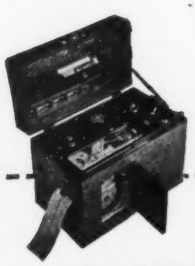

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1. Frost, L. H., and Jackson, R. L.: J. Pediat. 39: 585-592, 1951.

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